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PHARMACOLOGY OF MEDICINAL PLANTS AND NATURAL PRODUCTS

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1. Introduction

In recent times, focus on plant research has increased all over the world and a large body of evidence has collected to show immense potential of medicinal plants used in various traditional systems. More than 13,000 plants have been studied during the last 5 year period. The present review aims to compile data generated through the research activity using modern scientific approaches and innovative scientific tools in last 5 year period *i.e.* 1994-1998.

To facilitate the readers to look at their areas of interest more easily, the data in the present review have been organised in various sections according to pharmacological activities. Two of these sections deserve special mention - one on nutraceutics, in which research on plants that form a part of our normal diet has been compiled irrespective of activity and the second on phytochemical studies which are associated with pharmacological activity. In the rest of the sections, the description on individual plants is followed by that on polyherbal formulations. Polyherbal formulations have been included as they are widely used, as reflected in the study by Karandikar *et al*,[1] and the data based on the studies carried out with these formulations has been published in peer-reviewed journals.

2. CNS Active Plants

The scope of CNS active Indian Medicinal Plants in therapeutics has been illustrated in a review article by Vaidya[2]. The following paragraphs focus on the further work carried out during the last 5 years.

2.1. Nootropics

Various extracts derived from the seeds of *Pongamia pinnata* (Karanj) decreased pentobarbitone sleeping time, probably by stimulation of the hepatic microsomal enzyme system[3]. Similar properties were exhibited by its roots. However, the petroleum ether extract (PEE) of the roots enhanced pentobarbitone sleeping time, probably due to CNS depression[4]. The PEE of the seed of *Pongomia pinnata* was further tested for nootropic activity in an experimental model of Alzheimer's disease (created by ibotenic acid induced lesioning of nuclear basalis magnocellularis). It reversed both, the cognitive deficits and the reduction in cholinergic markers after 2 weeks of treatment. Reversal of perturbed cholinergic function appears to be the possible mechanism[5].

The alcoholic extract of *Bacopa monniera* facilitated the acquisition, consolidation and retention of memory as seen by its effect on 3 newly acquired behavioural responses in albino rats, *viz*. foot shock motivated brightness discrimination, active conditioned avoidance and Sidman continuous avoidance responses. Further studies identified the chemical constituent, a mixture of 2 saponins designated as bacosides A & B, responsible for the facilitatory effect of *Bacopa monniera* on learning schedules. The bacosides also attenuated the retrograde amnesia produced by immobilisation induced stress, electroconvulsive shock and scopolamine and enhanced protein kinase activity and increased the protein content in the hippocampus. Phase I clinical studies have confirmed the safety of the bacosides in healthy male volunteers at both single and multiple doses administered over a period of 4 weeks[6].

The acetone soluble fraction of petroleum ether extract of *Lawsonia inermis* (Mehendi) leaves showed significant nootropic effect on the elevated plus maze and passive shock avoidance paradigms. The extract also potentiated clonidine induced hypothermia and decreased lithium induced head twitches. This indicates that it affects 5HT and noradrenaline mediated

behaviour. It had no effect on haloperidol induced catalepsy, thus showing no effect on dopamine mediated behaviour[7].

A lot of attention has been focused on the effect of BR-16A (Mentat), a polyherbal formulation, on learning and memory. It has been shown to augment acquisition and retention of learning in normal rats, as well as in states of cognitive deficits induced by variety of insults including pre-natal undernutrition, post-natal environmental impoverishment, sodium nitrite hypoxia, aluminium, increasing age and electroconvulsive shock (ECS) induced antero-grade and retro-grade amnesia[8-10]. Ramteke,*et al*,[11] demonstrated that administration of BR-16A to slow learning rats, improved learning (both speed and magnitude) on the Hebb Williams complex maze as compared to control. The results indicated that BR-16, like piracetam, could facilitate learning and memory, and could be categorized as a nootropic agent.

Bhardwaj and Srivastava[12] have shown that Mentat (designated by them as CIHP III), significantly improved the avoidance learning during endurance performance in rats when tested on the Runimex, a circular runaway. The number of stimuli *i.e.* electrical shocks required to induce learning were considerably reduced in the treated animals.

Trasina, a polyherbal formulation, was found to exert significant nootropic effect following 21 days therapy in 2 experimental models of Alzheimer's disease. These models were induced in rats by either injecting colchicine (15 µg/rat) intra-cerebroventricularly (*i.c.v.*) or lesioning of nucleus basalis magnocellularis by ibotenic acid (10 µg/rat). Trasina improved both memory and levels of various cholinergic markers like acetylcholine concentration, choline acetyl transferase activity and muscarinic cholinergic receptor binding in frontal cortex and hippocampus of rat brain. Thus its nootropic effect may be attributed to correction of cholinergic dysfunction[13].

Pre-treatment with Memorin (200 mg/day/kg), another herbal formulation, was found to attenuate electroconvulsive shock induced retrograde amnesia in rats when tested for passive avoidance learning paradigms in a shuttle box[14].

2.2. Psychoactives

The leaf extract of *Azadirachta indica* (Neem) exhibited anxiolytic effects comparable to diazepam at low doses (10-200 mg/kg), when tested in rats. Higher doses (>400 mg/kg) however, did not show anxiolytic activity[15].

Ethanol extract and cold aqueous infusion of *Vitex leucoxylon* (Nirnochi in Tamil) leaf depressed spontaneous motor activity, antagonised d-amphetamine induced sterotypy and oxotremorine induced tremors and shortened the duration of immobility in the behavioural 'despair' test in mice[16].

Methanolic extract of rhizomes of *Nelumbo nucifera* (Kamal) was found to cause significant reduction in spontaneous activity, decrease in the exploratory behavioural pattern by the head dip andY maze tests, muscle relaxant activity and potentiation of pentobarbitone induced sleeping time[17].

Mitra, *et al*, [18] have shown that the root powder of *Panax ginseng* did not affect pentobarbitone sleep time or spontaneous motor activity. Although it potentiated amphetamine induced increase in motility, it attenuated the other effects of amphetamine, *viz*. stereotypy and lethality in aggressive mice. Haloperidol catalepsy was potentiated while the behavioural responses of 5-hydroxytryptophan and l-dopa were both attenuated. It exhibited significant aggression-inhibiting effect in doses that had no effect on spontaneous movements. The results have been discussed on the basis of interaction of *Panax ginseng* with the functioning of various neurotransmitters.

All extracts [petroleum ether (PEE), benzene(BE), chloroform (CE), acetone (AE) and ethanol (EE)] of the leaf of *Abies pindrow* Royle (Silver fir) showed potentiation of pentobarbitone sleeping time *i.e.* CNS depressant effect. The PEE, BE, CE and AE (highest efficacy) showed significant anti-depressant activity. On the other hand, EE was found to potentiate immobility, suggesting that this fraction is devoid of anti-depressant effect [19].

Ginkgolic acid conjugates (GAC) (6-alkylsalicylates, namely n-tridecyl-, n-pentadecyl-, n-heptadecyl-, n-pentadecenyl- and n-heptadecenylsalicylates) isolated from the leaves of Indian *Ginkgo biloba* Linn., a PAF antagonist, showed consistent and significant anxiolytic activity. By contrast, EGb 761 and Ginkocer, 2 conjugates which are devoid of GAC, did not evoke significant activity. EGb 761 was found to increase rearing and decrease immobility time only in open field behaviour. This effect may be due to weak anti-anxiety activity[20].

Administration of BR-16A for 7 days induced dose related anxiolytic effects as assessed by paradigms like the open field and elevated plus maze tests in mice and the social interaction and Vogel's drink conflict tests in rats. It attenuated the increase in rat brain tribulin levels, a putative endocoid anxiety marker footshock - induced aggressive behaviour in paired rats but failed to affect clonidine-induced automutilative behaviour. Reduction in swim stress induced immobility in Porsolt's behavioural despair test, reduction in escape failures concomitant with an increase in avoidance response in the learned helplessness test and attenuation of muricidal behaviour in rats demonstrated that it possesses anti-depressant properties[21].

2.3. Agents attenuating dependence

Chronic treatment with the root extract of *Withania somnifera* (Ashwagandha) attenuated the development of tolerance and also the development of dependence to morphine in mice. By itself, *Withania somnifera* showed no analgesic effect[22].

2.4. Anticonvulsants

In a study carried out by Manocha, *et al* [23], *Ginkgo biloba* decreased the protective effect of sodium valproate and carbamazepine against picrotoxin as well as strychnine induced convulsions in mice. Further studies showed that pre-treatment with *Ginkgo biloba* extract potentiated the convulsions produced by picrotoxin and strychnine, indicating the involvement of GABAergic system and chloride channels (for picrotoxin) and modulation of action of the glycine neurotransmitter (for strychnine) by *Ginkgo biloba* [24].

Panax ginseng was shown to have no anticonvulsant action, nor did it potentiate the anticonvulsant effects of phenobarbitone and diazepam[18].

Chronic administration of BR-16A was found to protect against pentylenetetrazole (PTZ) induced kindling in mice, demonstrating the role of GABA receptor in PTZ induced kindling and protection by BR-16A by its interaction with these receptors[25].

Caffeine intake has been shown to increase the plasma half- life (2-fold) and reduce the bioavailability by 32% of carbamazepine in normal human volunteers. No interaction was seen with sodium valproate. These results indicate the need for restriction of xanthine/caffeine consumption in patients on carbamazepine therapy[26].

2.5. Sedatives

The non-polar fractions of the leaf of *Vernonia* species (Sahadevi) *viz*. *Vernonia lasiopus* and *Vernonia galamensis* have been shown to have sedative properties in rats[27].

2.6. Analgesics

Gossypin , a bioflavonoid from the yellow petals of *Hibiscus vitifolius* (Bhasadwaji), has been shown to have anti-nociceptive activity, similar to morphine and involving multineurotransmitter systems, mainly the cholinergic and GABAergic neurotransmitter pathways. Gossypin pre-treatment significantly decreased the development of acute tolerance to morphine induced anti-nociception (acetic acid induced writhing assay). Thus, it is a potential candidate for clinical trials as an analgesic with the advantages of lack of tolerance and dependence liability[28].

Suppression of acetic acid writhing was seen with both the ethanol extract and cold aqueous infusion of *Vitex leucoxylon* [16].

Azadirachta indica showed analgesic properties in mice. Pre-treatment with the opioid antagonist, naloxone and central noradrenaline depletor, DSP-4, attenuated the analgesia whereas the serotonin synthesis inhibitor, PCPA, potentiated the same, suggesting that both central and peripheral mechanisms and complex neural pathways (opioid and non-opioid *i.e.* monoaminergic) may be involved in this effect[29].

Cerpegin, a novel furopyridine alkaloid isolated from Ceropegia *juncea Roxb.* (Bhutumbi), has shown an analgesic effect (not involving the opioid pathway) against acetic acid induced writhing in mice[30]. Using the same model in rats, significant analgesic activity was detected in leaf and seed of *Vernonia lasiopus* and *Vernonia galamensis* [27] and alcoholic extract of *Ochna obtusata* (Kanakchampak) stem bark[31]. *Panax ginseng* exhibited anti-nociceptive activity and potentiated the anti-nociceptive activity of both pentazocine and aspirin[18].

The PEE, BE and EE of the roots of *Pongamia pinnata* showed significant analgesic effect in the tail flick test[4]. The PEE and direct EE of the seeds also showed[3] significant analgesic activity at doses higher than 100 mg/ kg.

Different extracts of *Abies pindrow* Royle leaf (PEE,BE,CE,AE and EE) showed significant analgesic effect in the hot wire induced tail flick response in rats. Possible mechanism of action could be its inhibitory effect on PAF and prostaglandins as this plant contains phyto-constituents such as flavonoids and terpenoids[19].

Alcoholic extract of the roots of *Clerodendron serratum* (Bharanji) showed significant analgesic activity in mice[32].

2.7. Anti-inflammatory agents

The ethanolic extract of the leaf of *Vitex leucoxylon* showed significant inhibition of carrageenin paw oedema and granulation tissue formation in rats[16].

The aqueous suspension of dried latex of *Calotropis procera* (Arka) showed anti-inflammatory property when tested in the carrageenin and formalin induced rat paw oedema models[33].

The roots and leaves of *Butea frondosa* (Palash) were evaluated for ocular anti-inflammatory activity in rabbits. The results showed that the gel formulation of *Butea frondosa* leaves, prepared using a commercially available, pluronic F-127, reduced the intra-ocular pressure, decreased leucocytosis and miosis and was comparable to flubiproten gel[34].

The triglyceride fraction of oil of *Ocimum sanctum* (Tulsi) offered higher protection against carrageenin induced paw oedema in rats and acetic acid induced writhing in mice, as compared to the fixed oil [35]. Fixed oil of *Ocimum sanctum* and linolenic acid were found to possess significant anti-inflammatory activity against PGE_2, leukotriene and arachidonic acid induced paw oedema. The anti-inflammatory activity of linolenic acid present in the fixed oil of *Ocimum sanctum* was probably due to blockade of both, the cyclo-oxygenase and lipo-oxygenase pathways of arachidonic acid metabolism[36].

Alcoholic extract of *Ochna obtusata* stem bark demonstrated potent anti-inflammatory effects in the rat paw oedema and cotton pellet granuloma models[31].

All extracts of the root of *Pongamia pinnata* showed significant anti-inflammatory activity (compared to phenylbutazone) in carrageenin and PGE_1 induced oedema models. Possible mechanism of action could be prostaglandin inhibition, especially by EE and AE. The BE was effective in carrageenin but not the PGE_1 model of inflammation. The anti-inflammatory property appears to reside mainly in the intermediate polar constituents and not in lipophilic or extremely polar constituents[37].

The PEE and CE of the seeds of *Pongamia pinnata* showed potent acute anti-inflammatory effect whereas the aqueous suspension showed pro-inflammatory effects. Further studies have shown that maximum anti-inflammatory effect was seen in the bradykinin induced oedema model with the direct EE[38]. Possible mechanism of action could be inhibition of prostaglandin synthesis and decreased capillary permeability. PEE and AE inhibited histamine and 5- hydroxytryptamine induced inflammation probably by their lipophilic constituents preventing the early stages of inflammation. However, the fractions were not effective against Freund's adjuvant arthritic model. The latter finding indicates that the plant may not be effective in rheumatoid arthritis.

All extracts of *Abies pindrow* Royle leaf showed anti-inflammatory effect in various animal models of inflammation such as carrageenin induced paw oedema, granuloma pouch and Freund's adjuvant arthritis. Chemical analysis indicated the presence of glycosides and steroids in the PEE and BE and terpenoids and flavonoids in the AE and EE. Flavonoids and terpenoids are polar substances effective in acute inflammation whereas glycosides and steroids are non-polar substances effective in chronic inflammation[39].

The methanolic extracts of the flowers of *Michelia champaca* Linn. (Champaka), *Ixora brachiata* Roxb (Rasna) and *Rhynchosia cana* Willd were found to possess significant anti-inflammatory activity against cotton pellet induced subacute inflammation in rats. The latter 2 drugs showed higher activity as compared to *Michelia champaca*. They also reduced the protein content, acid phosphatase, glutamate pyruvate transaminase and glutamate oxaloacetate transaminase activities in the liver and serum. These properties are probably due to the presence of flavonoids in the flowers of these plants[40].

The methanolic extract of the aerial part of *Sida rhombifolia* (Atibala) showed significant oedema suppressant activity in the carrageenin induced paw oedema model in rats. Probable mechanism of

action may be due to its inhibitory effects on release of mediators of inflammation such as histamine, 5-hydroxytryptamine, bradykinin *etc*[41].

Gmelina asiatica (Gopabhadra) root powder was effective in reducing the oedema in the carrageenin-induced rat paw oedema model of acute inflammation. When tested against the cotton pellet granuloma model of chronic inflammation, it not only reduced the weight of the granuloma but also the lipid peroxide content of granuloma exudate and liver and gamma-glutamyl transpeptidase in the granuloma. It also normalised serum albumin and serum acid and alkaline phosphatase levels. Probable mechanism of its anti-inflammatory effect may be its anti-proliferative, anti-oxidative and lysosomal membrane stabilising effects[42].

Studies have shown that, the methanol extract of *Nelumbo nucifera* rhizome as well as the steroidal triterpenoid isolated from it (betulinic acid), possessed significant anti-inflammatory activity when evaluated in the carrageenin and 5-hydroxytryptamine induced rat paw edema models. The effects produced were comparable to that of phenylbutazone and dexamethasone[43].

The water soluble part of the alcoholic extract of *Azadirachta indica* exerted significant anti-inflammatory activity in the cotton pellet granuloma assay in rats. Levels of various biochemical parameters studied in cotton pellet exudate were also found to be decreased *viz*. DNA, RNA, lipid peroxide, acid phosphatase and alkaline phosphatase suggesting the mechanism for the anti-inflammatory effect of *Azadirachta indica*[44].

Alcoholic extract of the roots of *Clerodendron serratum* showed significant anti-inflammatory activity in the carrageenin induced paw oedema and cotton pellet granuloma models in rats[32].

The aqueous extract of *Gymnema sylvestre* leaves showed significant anti-inflammatory activity in the carrageenin induced rat paw oedema and mouse peritoneal ascitis models. It, however, did not inhibit granuloma formation and related biochemical indices, such as hydroxyproline and collagen, (as seen in the pith granuloma model) thus indicating that it did not interfere in the normal healing process. In addition, the extract did not affect the integrity of the gastric mucosa, even at high doses, thus appearing to be a less gastrotoxic anti-inflammatory agent as compared to other non-steroidal anti-inflammatory agents[45].

Sandhika, an Ayurvedic drug used in the treatment of rheumatoid arthritis showed significant anti-inflammatory activity when tested against carrageenin induced paw oedema and cotton pellet granuloma. Possible mechanism of action could be by free radical scavenging activity[46].

Treatment with Ease, a polyherbal formulation, significantly reduced Freund's adjuvant-induced non-established and established arthritis in rats. *In vitro* too, it provided significant protection against protein denaturation and RBC membrane damage and exhibited significant proteinase inhibitory action, thus indicating its possible use as an anti-arthritic[47].

Jigrine, another polyherbal formulation, exhibited anti-inflammatory activity against carrageenin induced acute inflammation but not against cotton pellet granuloma (subacute inflammation). Effect on biochemical parameters suggested that the mechanism of its anti-inflammatory effect could be in its antioxidant and membrane stabilising effect[48].

2.8. Antipyretics

The ethanolic extracts of *Ailanthus excelsa* (Mahanimba), *Toddalia asiatica* (Kanchana) and *Araucaria bidwilli* (Monkey puzzle) showed moderate to significant degree of antipyretic activity in an experimental rat model of 20% yeast suspension induced hyperthermia[49]. *Andrographis elongata* showed more potent antipyretic activity when compared to *Andrographis paniculata* (Kalmegha)[50]. Methanolic extract of rhizome of *Nelumbo nucifera* produced a significant dose dependent lowering of body temperature in normal rats and antipyretic effect in pyretic rats [51]. *Rhynchosia cana* showed significant antipyretic activity in rats[40]. Alcoholic extract of the roots of *Clerodendron serratum* showed significant antipyretic activity following typhoid TAB vaccination in rabbits[32].

The antipyretic activity of TBR-002, a herbal formulation, was found to be almost equal to paracetamol in a rat model of pyrexia induced by subcutaneous injection of 15% yeast suspension[50].

As against these antipyretic plants, *Panax ginseng* showed hyperthermic effect and attenuated the

hypothermic response of reserpine and 5-HTP induced hyperthermia in animals[18].

2.9. Neurotransmitter modulation

Investigation of the neurochemical effects of different fusarial toxins elaborated from *Fusarium moniliform* and *Fusarium orysporum* showed that *Fusarium moniliform* had irreversible and nonspecific MAO inhibitory activity comparable to nialamide[52].

Studies on the effect of BR-16A on adrenergic and dopaminergic functioning in rats showed that it did not interfere with α_2 -adrenergic and dopamine autoreceptor functioning. However, its effects on mobility in the open field test following challenge with clonidine or apomorphine showed that it enhanced dopamine post-synaptic receptor activity[53].

3. Plants modulating autonomic and autacoid activity

Over the years, the trend to evaluate agents modulating autonomic and autacoid activity is declining. However, importance of using certain methodologies like isolated tissue experiments to gather preliminary data regarding interaction of a plant product with host receptor systems remains unquestionable. Following are some of the attempts in this direction.

The effects of stem extract of *Cuscuta reflexa* (Amarvalli) resembled those of acetylcholine when tested on isolated rabbit ileum, frog rectus abdominis and heart and these effects were blocked by atropine. Effect of the extract on isolated frog rectus abdominis muscle was blocked by pancuronium and potentiated by neostigmine[54].

Hot water extract of *Camellia sinensis* (Green tea leaf extract, GTE) had a facilitatory effect at lower concentrations and a paralytic effect at higher concentrations on skeletomotor function but did not have any effect on direct twitch responses or on acetylcholine and KCl induced contractures of denervated rat diaphragm. In addition it antagonised the submaximal paralytic effect of d-tubocurarine and decamethonium. The effects of GTE were nullified in the presence of magnesium chloride. Since nifedipine reduced GTE-induced facilitation as well as inhibition of twitch responses, it has been suggested that GTE might act on Ca^{2+} channels at the skeletomotor junction. The effect of crude polyphenol of GTE on neuromuscular junctions was found to be similar to that of GTE suggesting that the crude polyphenol content of GTE was the active constituent responsible for its effect on neuromuscular junction[55].

Beta-adrenoreceptor mediated tracheal relaxation or the decreased responsiveness of the tracheal smooth muscle induced by down-regulation of receptors with terbutaline in guinea pigs was unaffected by Abana, a herbomineral formulation. This is probably due to lack of Abana's effects on ß-receptors of the airway. However, pretreatment with Abana increased potassium chloride-induced contractions and increased the sensitivity to the relaxant effects of isoprenaline, terbutaline and aminophylline following such contractions, probably by enhancing membrane permeability to calcium ions[56].

4. CVS active plants

Research in cardiovascular pharmacology in the past few years has been mainly focused on agents with hypolipidaemic properties and plant drugs are no exception. This section describes various agents that have been evaluated for their effect on the cardiovascular system.

4.1. Anticoagulant

The petroleum ether and methanolic extracts of the leaf and oleoresin of *Araucaria bidwillii* showed marginal delaying effect on bleeding and clotting times at 1 hour interval in rabbits when tested using Wright's and Dukes capillary tube method[57].

4.2. Hypolipidaemics

The ethanol extract and cold aqueous infusion of *Vitex leucoxylon* leaf lowered serum total cholesterol levels in mice[16].

Gugulipid (an active principle of *Commiphera mukul*) is an agent that has been widely investigated for its hypolipidaemic activity. Co-administration of gugulipid with propranolol or diltiazem in normal volunteers was found to decrease the bioavailability of both drugs[58].

Dried flowers of *Adenocalymma alliaceum* when fed at 2% level for 6 weeks to hypercholesterolaemic rats, lowered serum cholesterol levels significantly, lowering the absorption of dietary cholesterol from the intestines[59].

Semecarpus anacardium (Bhallatak, nut shell) extract also exhibited hypocholesterolemic action and prevented cholesterol induced atheroma in hypercholesterolaemic rabbits[60]. Similarly, *Terminalia belerica* (Bibhitak) reduced the levels of lipids in experimentally induced hypercholesterolaemia in rabbits. There was also a significant decrease in liver and heart lipids[61].

Administration of ethanolic extract (50% v/v) of *Plumbago zeylanica* (Chitrak) root, alone and in combination with vitamin E, significantly reduced serum total cholesterol, LDL cholesterol and triglyceride levels in experimentally induced hyperlipidaemic rabbits[62]. However, Dwivedi[63] pointed out that the ethanolic extract of *Plumbago zeylanica* root alone and with vitamin E lowered HDL cholesterol levels as well. Hence, he has advised caution about its use in patients and confirmation of these findings through larger sample size studies.

Administration of cell culture extract of *Hemidesmus indicus* (Sariva) in rats also receiving an atherogenic diet prevented hypercholesterolaemia[64].

4.3. Anti-hypertensives

Preparation of the whole plant of *Phyllanthus amarus* (Bhuiamalaki) was administered to 9 mild hypertensive subjects for 10 days. The results suggest that it is a potential diuretic, hypotensive and hypoglycemic drug for humans[65].

Hydroalcoholic leaf extract of *Azadirachta indica* caused a dose-dependent hypotensive effect. It did not alter the force of contraction or heart rate at low doses in isolated frog heart, but caused a temporary cardiac arrest in diastolic at high doses[66].

The petroleum ether extract of *Abies pindrow* leaf showed significant hypotensive effect in anaesthetized dogs[19].

Treatment with Abana, a polyherbal formulation, in normotensive rats produced significant lowering of blood pressure, enhancement of vaso-pressor responses to low dose of noradrenaline (with no effect on dopamine β hydroxylase activity) and no effect on the vaso-depressor responses of acetylcholine and isoprenaline. It, however, protected against ethinyl oestradiol induced hypertension and increased dopamine β hydroxylase activity in these hypertensive animals, thus suggesting that it produces effects against ethinyl oestradiol induced hypertension by its sympatholytic property[67].

4.4. ACE (angiotensin converting enzyme) inhibitors

Seventy- five species of traditional medicinal plants belonging to 42 families have been investigated for their ability to inhibit the angiotensin converting enzyme. Of these, 4 species were found to possess a high ACE inhibiting ability and were low in their tannin content[68].

4.5. Cardio-protectives

Rutin, a flavonoid, obtained from the plant, *Sophora japonica*, markedly reduced the infarct size and prevented the loss of the 'R' wave in anaesthetized rats subjected to coronary artery ligation. It, however, had no effect on heart rate and systolic blood pressure. It also reduced the ligation-induced increase in serum malonyldialdehyde levels and prevented the loss of glutathione peroxidase activity. Rutin inhibited, *in vitro*, luminol-induced chemiluminescence of rat PMN's, thus indicating that its beneficial effect is probably due to its ability to impair the generation of reactive oxygen species[69].

4.6. Positive ionotropics

Vaidya[70] in his editorial, had raised the issue on the controversies that exist regarding ionotropic actions of *Terminalia arjuna* (Arjuna). Though there are studies proving positive ionotropic effects of this plant, some scientists have observed negative ionotropic and chronotropic effects as well. Hence, he had advised more detailed experimental and clinical studies on the plant and its active principle. Data of placebo-controlled clinical studies carried out subsequently with this plant is presented below.

When the bark extract of *Terminalia arjuna* was compared to placebo in 12 patients with refractory CCF in a phase II clinical trial, it was observed that treatment with *Terminalia arjuna* was associated with an improvement in symptoms and signs of heart failure, improvement in the NYHA class (from IV & III), decrease in echo-left ventricular end-diastolic and end-systolic volumes indices, increase in the left ventricular stroke volume index and increase in left ventricular ejection fraction at the end of 2 weeks. Long term therapy (*i.e.* 24 months) too showed continued

improvement in the signs and symptoms, effort tolerance and NYHA class among the patients[71].

Dwivedi and Jauhari[72] studied the effects of bark stem powder of *Terminalia arjuna*, as compared to placebo, on angina pectoris, CCF and left ventricular mass in 12 patients of myocardial infarction with angina and/or ischaemic cardiomyopathy. Their findings indicate the potential of *Terminalia arjuna* improving left ventricular ejection fraction and reducing left ventricular mass in coronary artery disease.

5. Plants acting on respiratory system

Methanolic extracts of *Drymaria cordata* willd and *Leucas lavandulaefolia* (Dronapushpi) were investigated for their effects on a cough model induced by sulfur dioxide gas in mice. Both exhibited significant anti-tussive activity, comparable to that of codeine phosphate and increasing concentrations showed better inhibition of cough[73,74].

Solanum xanthocarpum (Kantakari) and *Solanum trilobatum* (Alarka), the plants mentioned in Siddha, have been shown to improve various parameters of pulmonary function (FVC, FEV_1, PEFR & FEF25-75%) in asthmatic subjects with mild-moderate asthma[75].

6. Anti-allergic plants

Ethanolic extract of *Vitex negundo* (Nirgundi) of was found to inhibit immunologically induced degranulation of mast cells better than that with compound 40/80. It also inhibited be oedema during active paw anaphylaxis in mice[76]. Nair and Saraf [77] further studied their effects on mediator release and smooth muscle contractions of sensitized and non-sensitized guinea pig trachea using antigen and compound 48/80 respectively. The extract significantly inhibited both the initial and later sustained phases of tracheal contractions. The initial phase was primarily due to histamine release which was blocked by the extract (confirmed in guinea pig ileal studies). The latter phase was due to release of lipid mediators from arachidonic acid. Inhibition of the latter phase may be secondary to inhibition of arachidonic acid by the ethanolic extract.

Arbortristoside A & C, derived from the alcoholic extract of the seeds of *Nyctanthus arbortristis* (Parijat)[78], two diterpenes, andrographolide and neoandrographolide, isolated from *Andrographis paniculata*[79], and Himachalol, a sesquiterpene alcohol, derived from the hexane soluble extract of the wood of *Cedrus deodara* (deodar) [80], were found to possess significant anti-allergic activity comparable to disodium cromoglycate when tested in the experimental models of passive cutaneous anaphylaxis and mast cell degranulation in rats.

Similarly, hot aqueous extract of the bark of *Albizzia lebbeck* (Shirish) was found to possess anti-allergic properties in experimental model of passive cutaneous anaphylaxis and mast cell stabilization activity[81].

7. Hypoglycemic plants

A preparation of the whole plant of *Phyllanthus amarus* was found to have hypoglycemic effects in 9 human subjects, 4 of whom were diabetics[65].

In vitro studies carried out by Rizvi *et al*,[82] have shown that epicatechin, an active constituent of *Pterocarpus marsupium* (Vijaysar)exerted a protective effect on erythrocyte osmotic fragility, similar to insulin, but by a different mechanism of action.

In streptozotocin induced diabetic rats, of the 3 important phenolic constituents of the heartwood of *Pterocarpus marsupium* (*viz*.pterosupin, marsupin and pterostilbene) marsupin and pterostilbene significantly lowered the blood glucose levels and the effects were comparable to metformin[83]. The hypoglycemic efficacy of *Pterocarpus marsupium* has been further evaluated in a multicentric (4 centres) flexible-dose open trial in newly-diagnosed patients of non-insulin-dependent diabetes mellitus[84]. Control of blood glucose (both fasting and post-prandial levels) was attained in 67 of 97 patients (69%) studied in 12 weeks and the optimum dose was 2 g of the extract. HbA_1c values also decreased significantly. No significant change was observed in the mean levels of lipids.

The chloroform eluted fraction of the petroleum ether extract of the root bark of *Salacia oblonga* Wall (Ponkoranti) and a fluorescent compound separated from it (by TLC) demonstrated hypoglycemic potency in rats when compared to tolbutamide[85].

The alcoholic extract of *Inula racemosa* (Pushkarmula) lowered blood glucose and enhanced liver glycogen in rats. However, there was no increase in plasma insulin levels nor an increase in the degree of degranulation of beta cells of pancreas. Its

action may be at the peripheral level by potentiating insulin sensitivity[86].

Hot water extract of *Camellia sinensis* (Black tea leaf) significantly reduced the blood glucose level and was found to possess both preventive and curative effects in streptozotocin induced diabetic rats[87].

The leaf extract of *Azadirachta indica* had no effect *per se*, on the peripheral utilization of glucose (determined by intravenous glucose tolerance tests) and on hepatic glycogen in normal and streptozotocin induced diabetic rats. However, it blocked the effects of epinephrine on glucose metabolism and reduction in peripheral glucose utilization in diabetic rats and to some extent in normal rats, indicative of an anti-hyperglycemic potential of the plant[88].

Leaf extract of *Aegle marmelos* (Bilva) was found to significantly reverse the raised K_m values, but not V_{max} values of the enzyme malate dehydrogenase, an important enzyme in glucose metabolism, in streptozotocin induced diabetic rats. Alteration in the qualitative and quantitative nature of the enzyme has been suggested to contribute to the pathological state of diabetes. The leaf extract was also effective in restoring blood glucose and body weight to normal values[89]. In another study[90], leaf extract of *Aegle marmelos* significantly reversed the altered (histological and ultrastructural) parameters in tissues of streptozotocin induced diabetic rats seen by light and electron microscopy to near normal and improved the functional state of pancreatic beta cells. The hypoglycemic effects of this plant drug thus appears to be mediated through regeneration of damaged pancreas.

Oral administration of the methanolic extract (but not the water extract) of aerial parts of *Artemisia pallens* (Daman) led to significant blood glucose lowering in glucose fed hyperglycemic and alloxan induced diabetic rats. Increased peripheral utilisation of glucose is probably the mechanism responsible. Inhibition of renal proximal tubular reabsorption of glucose may also contribute[91]. Saxena *et al* [92] compared the effects of mode of action of 3 structurally different hypoglycemic agents, tolbutamide, centpiperalon and a swerchirin- containing fraction (SW1) from the plant *Swertia chirata* (Chirayata) in normal and streptozotocin induced mild and severe diabetes in rats. Except in rats with severe pancreatic damage, SW1 showed better blood glucose lowering effect compared to tolbutamide.

Ocimum album (Holy basil) leaves significantly decreased the fasting and post-prandial blood glucose levels in patients with NIDDM in a randomized, placebo-controlled, crossover, single blind trial[93]. Administration of *Ocimum sanctum* leaf powder to normal and diabetic rats for a period of one month resulted in a significant reduction in fasting blood sugar, uronic acid, total amino acids, total cholesterol, triglyceride, phospholipids and total lipids. Total cholesterol, triglyceride and total lipids were significantly lowered in the liver, kidney and heart. They indicate the hypoglycemic and hypolipidemic effect of *Ocimum sanctum* in diabetic rats[94].

Chronic administration of *Prunus amygdalus* (Almond) seeds and its proportionate fractions *viz*. defatted seed and oil to rabbits demonstrated a definite hypoglycemic effect. The active factor seems to be a non-oil fraction which is only partly soluble in ethyl ether[95].

Significant hypoglycemic effect was observed with 1500 mg/kg dose of juice of leaves of *Lantana camara* in rats[96].

The protective effect of *Capparis decidua* (Karir) powder on oxidative stress and diabetes in alloxan induced diabetic rats has been evaluated. The data indicate that *Capparis decidua* may have a potential use as an anti-diabetic agent, especially in chronic cases as it helps in lowering the oxidative stress in diabetes[97].

Dubey *et al*,[98] studied the effect of D-400, a polyherbal formulation, on blood glucose, blood urea and serum creatinine in alloxan-induced diabetic rabbits. D-400 significantly prevented the rise in blood urea and serum creatinine levels at the end of 36 weeks, thus showing promise against alloxan induced renal damage. The rise in blood sugar too in the treated group was lower than the saline control. Further studies by Dhawan *et al*,[99] demonstrated that D-400, in diabetic rats, not only brought the raised blood glucose levels to within normal limits and raised the suppressed glycogen levels, but also brought towards normal, the decreased ^{14}C glucose uptake by liver slices in *in vitro* studies.

Trasina, an Ayurvedic herbal formulation, significantly reduced streptozotocin induced hyperglycemia and also attenuated streptozotocin induced decrease in superoxide dismutase activity of pancreatic islet cells in male Charles Foster rats[100].

8. Anti- and pro-fertiliy plants

The second area which has been widely worked upon in the field of endocrinology is the reproductive system.

Ethanolic extract of *Bupleurum marginatum* was found to have significant oestrogenic activity as seen by the increased uterine weight and early opening and cornification of vagina in immature rats and histological features of the uterus[101].

Praneem vilci, a highly purified oil of *Azadirachta indica* seed, was found to be safe when administered as a single intra-uterine instillation in 18 healthy tubectomised women. No untoward effects were observed. The menstrual pattern and ovulatory status remained unaltered and the endometrial biopsy was normal. In 10 of the above women who had also received the HSD-hCG vaccine, co-administration of Praneem vilci did not prevent the antibody response to HSD-hCG vaccine[102]. The leaves of *Azadirachta indica* were found to have a reversible, anti-androgenic properties in male rats[103].

Ethanolic extract of *Trichopus zeylanicum* (Arogyapacha in Tamil) leaf, when administered to male mice was found to stimulate sexual behaviour as evidenced by an increase in number of mounts and mating performance. Chronic administration of the drug was more effective than a single dose. The pups fathered by drug treated mice were also found to be normal with respect to foetal growth, litter size and sex ratio[104].

Benzene extract of *Hibiscus rosea* sinensis (Jaswand) flowers showed differing results when administered to adult and immature mice. In the adults, it resulted in an irregular estrous cycle with prolonged estrous and metaestrous. An increase in the atretic follicles and absence of corpora lutea indicated the antiovulatory effect of the extract. However, in immature mice, the extract showed oestrogenic activity as seen by the early opening of the vagina, premature cornification of vaginal epithelium and increase in uterine weight[105].

9. Plants promoting skin and bone healing

Methanolic extract of *Cissus quadrangularis* (Asthishunkala) promoted the healing process of experimentally fractured radius-ulna of dogs as evidenced by radiological and histopathological examinations[106]. The treated group also exhibited a reduction in serum calcium levels as compared to saline control animals.

Intra-dermal administration of the essential oils from the leaves of Eucalyptus hybrid and seeds of *Seseli indicum* increased cutaneous capillary permeability when tested in Evan's blue treated rabbits. This effect may be beneficial in their probable wound healing activity[107].

Topical application of aqueous extract of latex of *Euphorbia neriifolia* (Nivadung) facilitated the healing of surgically produced cutaneous wounds in guinea pigs as evidenced by an increase in tensile strength, DNA content, epithelialisation and angiogenesis[108].

Only the aqueous extract suspension in 5% propylene glycol of *Centenella asiatica* as compared to the other extracts (*viz*. alcoholic, petroleum ether, chloroform, propylene glycol and glycosidal extract) promoted wound healing in experimentally induced open wounds on topical administration in rats as evidenced by the increase in collagen content and thickness of epithelium[109]. However, Suguna *et al*,[110] demonstrated that the alcoholic extract (oral and topical) of *Centenella asiatica* improved the rate of wound healing in rats. Sunilkumar *et al*,[111] showed that topical administration of the aqueous extract increased cellular proliferation, promoted collagen synthesis at the wound site as evidenced by the increase in DNA, protein and collagen content of granulartion tissue and in tensile strength. The treated wound epithelialised faster and the rate of wound contraction was higher as compared to control. Among the various formulations (ointment,cream and gel) of the aqueous extract, the process of healing was better with the gel formulation.

The extracts of four plants *i.e.* the leaves of *Aloe vera*, root and root bark of *Aegle marmelos* and *Moringa oleifera* and leaves of *Tridax procumbes* were found to promote wound healing in both normal and immunocompromised (steroid treated) rats in a space wound model. The plants increased not only lysyl

oxidase activity but also, protein and nucleic acid content in the granuloma tissue thus indicating that the plants probably exert their action at the cellular (nuclear) level. The plants also increased the tensile strength of the granuloma tissue probably as a result of the increase in the glycosaminoglycan content. Thus the plants not only hastened normal healing, but also reversed steroid depressed healing [112].

Sunder vati, an Ayurvedic formulation was effective in the treatment of acne vulgaris as seen by the significant reduction in lesion count in patients with this condition[113].

10. Plants acting on genito-urinary system

Ethanolic extract of *Ammannia baccifera* (Bhatjambol) was found to be effective in reducing the formation of urinary stones (prophylactic) as well as dissolving pre-formed ones (curative) that were induced by implantation of zinc discs in the urinary bladders of rats. The stones formed were mainly of magnesium ammonium phosphate with traces of calcium oxalate. Treatment with *Ammannia baccifera* also significantly reduced calcium and magnesium levels[114].

Lupeol and a number of its derivatives derived from *Crateva nurvala* (Varun) were found to possess significant anti-hyperoxaluric and anti-hypercalciuric activity when tested in rats against hydroxyproline induced hyperoxaluria and calciurial[115].

11. Gastro-intestinal pro- and anti-kinetic plants

The methanolic extract of rhizomes of *Nelumbo nucifera* showed significant inhibitory activity against castor oil induced diarrhoea and PGE_2 induced entero-pooling in rats. It also showed significant reduction of gastro-intestinal motility in rats, thus indicating its efficacy as an anti-diarrhoeal agent[116].

Three different dosage formulations (aqueous extract, dry powder and incinerated powder) of *Emblica officinalis* (Amalki) were evaluated for their effect on gastro-intestinal motility at different dose levels (210,420 and 840 mg/kg) in mice. The dry powder and the aqueous extract showed pro-kinetic effect at all the 3 dose levels. The incinerated powder at lower doses, showed pro-kinetic effect, whereas at higher doses, it decreased gastro-intestinal motility[117].

12. Cytoprotective plants

12.1. Ulcero- protectives

12.1.1. Gastric and duodenal ulcers

The alcoholic, oleoresin and petroleum ether extracts of leaf of *Araucaria bidwillii* showed moderate degree of ulcero-protective activity in pylorus ligated rat model of gastric ulceration[58].

Leaf and seed extracts of *Vernonia lasiopus* and *Vernonia galamensis* had antiulcerogenic effects when tested using either hydrochloric acid or ethanol as the necrotising agent in rats[27].

The protective effect of hot water extract of black tea (*Camellia sinensis*) was demonstrate on ulcers induced in rats by various ulcerogens (NSAIDs, ethanol, reserpine, 5-HT, histamine) and by cold restraint stress 5-HT and histamine. It altered the acid and peptic activity of gastric secretion[118].

All four sitavirya plants *viz*. Satavari (*Asparagus racemosus*: fresh root juice, 1250 mg/kg), Yastimadhu (*Glycerrhiza glabra*: water decoction of root, 600 mg/kg), Kutaja (*Holorrhena antidysentrica* : water decoctions of bark, 400 mg/kg) and Aswattha (water decoctions of bark, 500 mg/kg) were were found to have ulcero-protective effects against 2 hr cold restraint stress ulcers, pylorus ligation-induced gastric and cysteamine-induced duodenal ulcers in rats. However, they were ineffective against acute aspirin-induced gastric ulcers[119].

All extracts of the seeds of *Pongamia pinnata* showed significant anti-ulcerogenic effect in fasting mice[3]. The petroleum ether(PEE), benzene and ethanolic(EE) extracts of the root of the same plant showed significant anti-ulcerogenic effect in the pylorus ligated rat ulcer model. The EE but not PEE decreased acid pepsin secretion and increased mucus secretion. PEE showed significant CNS depression as mentioned earlier, thus probably relieving stress induced ulceration[4].

Bergenin and norbergenin, two isocoumarins, isolated from the leaves and roots of *Flueggea microcarpa* and luvangetin, a pyranocoumarin isolated from the seeds of *Aegle marmelos* Correa, gave significant protection against pylorus ligation- and aspirin-induced gastric ulcers in rats and cold restraint-induced gastric ulcers in rats and guinea pigs. The

gastro-protective effects of bergenin and norbergenin could be due to increased prostaglandin production as demonstrated using human colonic mucosal incubates. This mechanism was not responsible for the observed effects of luvangetin as it did not affect prostaglandin production[120].

All extracts (petroleum ether, benzene, chloroform, acetone and ethanolic) of *Abies pindrow* leaf showed ulcero-protective effect in a model of cold restraint stress because of their anti-stress effects. The extracts contained terpenoids and flavonoids which were shown to have marked inhibitory effect on PAF. Flavonoids have also been shown to increase mucus secretion, prostaglandin synthesis and blood flow[19].

Pretreatment with the aqueous extract of *Emblica officinalis* protected against ethanol- induced and cold restraint- induced gastric damage in rats (evaluated by the Evan's blue method) [117].

Cauvery 100, a polyherbal formulation, showed anti-ulcerogenic activity when tested against indomethacin induced ulcers in rats. It decreased the raised hexosamine and sialic acid levels in the ulcer towards normal, increased pepsin activity and gastrin levels and increased the uptake of titrated thymidine into the ulcer area, as compared to untreated animals[121].

Similarly, another polyherbal formulation, UL-409, demonstrated significant anti-ulcerogenic activity in three experimental studies carried out separately by Mitra *et al* [122], Vanisree *et al* [123] and Kulkarni and Goel[124].

12.1.2. Ulcerative colitis

Gupta *et al* [125] studied the protective effect of *Boswellia serrata* in patients suffering from (grade II and III) ulcerative colitis. The stool characteristics along with histopathological, scan microscopical changes in rectal biopsies and blood parameters (haemoglobin, serum iron, calcium, phosphorus, proteins, total leukocytes and eosinophils) improved following treatment with *Boswellia serrata* gum resin preparation; the results being similar to sulfasalazine.

12.2. Hepato-protectives

Two reviews have been published which cover most of the works carried out in this field. Vaidya *et al*, [126] have reviewed the experimental and clinical research work related to hepato-protective effects of various formulations available in the Indian market. Bhatt and Bhatt[127] have not only compiled the information available regarding the studies on various promising plant drugs from India but also have discussed the problems and pitfalls pertaining to this research. Some of the agents worth mentioning are as follows:

Tinospora cordifolia, a plant which has been shown to decrease fibrosis in rats, induced by CCl_4, was to significantly improved the suppressed Kupffer cell function in another rat model of chronic liver damage induced by heterologous serum. This raises the possibility that anti-fibrotic effect of *Tinospora cordifolia* is mediated through activation of kupffer cells[128]. When administered during the pre-operative period to patients with obstructive jaundice, it was found to decrease the post-operative morbidity and mortality (due to sepsis and liver cell failure). This was associated with bolstering of phagocytic and intracellular killing capacities of polymorphonuclear cells. Though *Tinospora cordifolia* was found to significantly decrease the complications associated with pre-operative biliary decompression *viz*. sepsis and immunosuppression, the prognosis was found to better when *Tinospora cordifolia* was instituted alone in preoperative period. These findings focus on the need to alter the preoperative management protocol for obstructive jaundice, by replacing the age-old procedure of biliary decompression by an immunomodulator[129]. The basis for improved prognosis appears to be the reduction in the incidence of endotoxaemia, as revealed from the studies in the rat model of cholestasis wherein *Tinospora cordifolia* was found to decrease the mortality in cholestatic rats. Earlier the therapy following cholestasis, better were the results[130].

Picroliv is a standardised preparation of irioid glycosides, picroside-1 and kutkoside obtained from *Picorrhiza kurroa.* Both picroliv and silymarin, a flavolignan component of *Silyburn marianum* seeds were shown to stimulate liver regeneration in the early stages when evaluated on partially hepatectomised rats. Both the drugs increased the levels of DNA, RNA, protein and cholesterol[131].

Picroliv administration in rats following exposure to alcohol resulted in lowering of various biochemical parameters of liver and serum that were elevated with alcohol consumption[132]. It protected against ethanol

(40%) induced toxicity in isolated rat hepatocytes[133]. I also showed a dose dependent hepatoprotective effect against oxytetracycline induced hepatic damage in rats[134]. The protective effect of picroliv against hepatic damage caused by *Plasmodium berghei* infection in *Mastomys caucha* was studied by Ramesh *et al*[135]. Treatment with this drug significantly reversed the changes in lipid metabolism induced by *Plasmodium berghei*. It reactivated the plasma and liver lipolytic enzymes, stimulated the binding of LDL with the liver receptors and enhanced the faecal excretion of bile acids, thus resulting in a return of circulatory lipoproteins towards normal.

Santra *et al*,[136] demonstrated that treatment with *Picrorrhiza kurroa* in carbon tetrachloride treated mice significantly reversed the altered serum ALT, AST, liver GSH, total thiol, glucose 6 phosphate dehydrogenase (G6PD), catalase and membrane bound Na^+/K^+ ATPase levels. Histopathological lesions of liver and lipid peroxidation were also significantly less in drug treated animals. Probable mechanism of action of *Picrorrhiza kurroa* appears to be its effect as a free radical scavenger and inhibitor of lipid peroxidation of liver plasma membrane.

The diterpenes, andrographolide, andrographiside and neoandrographolide, isolated from *Andrographis paniculata* demonstrated anti-oxidant effects in CCl_4 treated mice. Neoandrographolide was as effective as silymarin with respect to its effects on reduced glutathione, glutathione 5-transferase, glutathione peroxidase and superoxide dismutase and lipid peroxidation whereas andrographiside had mainly anti-lipoperoxidant activity[137]. Administration of the aqueous extract of *Andrographis paniculata* to mice suffering from liver damage induced by hexachlorocyclohexane (BHC) that ultimately leads to tumor formation, significantly lowered the raised enzymes (SGPT, SGOT, alkaline phosphatase) and raised the lowered protein concentration. The results confirm the hepato-protective property of *Andrographis paniculata* and suggest its probable role in delaying the hepatic tumorigenic condition[138].

Administration of Liv-52, a polyherbal formulation, significantly improved ethanol metabolism in a rat model of chronic alcohol administration[139]. It also prevented lipid peroxidation in CCl_4 induced liver damage as seen by a significant decrease in malondialdehyde content[140]. Both, Liv-52 and another formulation Kumaryasava were found to stimulate depressed hepatic enzyme activities such as hepatic arginase, cathepsin B, acid phosphatase and ribonuclease in CCl_4 induced liver damage indicating that these drugs have a protective effect on hepatic enzyme activity[141].

Liv. 100 is an improvised herbal formulation of Liv52. In an *in vitro* study combination of Liv52 and Liv100 reduced the peroxidation effect of hydrogen peroxide in rat liver homogenate. The protective effect of these drugs was attributed to the enhanced supply of reduced glutathione that inhibited the deleterious process of lipid peroxidation. This suggested the antioxidant potential of Liv. 52 and Liv. 100[142]. Simultaneous administration of Liv-100 with the anti-tubercular drugs, INH, rifampicin and pyrazinamide showed significant protection against hepato-toxic effects of the anti-tubercular drugs in rats[143].

The hepato-protective effect of Jigrine, an Unani polypharmaceutical herbal formulation containing 14 medicinal plants, was evaluated in 3 models of hepatic damage induced by either alcohol, carbon tetrachloride or paracetamol in rats. Jigrine significantly reduced the increased serum transaminases, bilirubin, prothrombin time and liver lipid peroxide content and also improved the histopathological findings. The authors have attributed its hepato-protective effect to its anti-oxidant property[144]. Further studies carried out on Jigrine by the same group showed that it also reduced the levels of gamma-GTP, triglycerides and lipid peroxides in the liver, confirming its membrane stabilising and antioxidant properties[145].

The importance of morphological features and time of collection of raw material can be understood from a study conducted by Rawat *et al*,[146] at the National Botanical Research Institute. The effect of seasons, root thickness and dosage forms (aqueous or powder) on the hepato-protective activity of *Boerrhavia diffusa* (Punarnava) was evaluated in thioacetamide intoxicated rats. Results showed that aqueous extract of roots of diameter 1-3 cms, collected in May (Summer) exhibited marked protection as determined by assessing serum enzymes *viz*. SGOT, SGPT, ACP and ALP, but not GLDH and bilirubin. Furthermore, the studies have shown that the aqueous form of the drug has more hepato-protective activity than the powder form, probably due to better absorption of the liquid form.

A novel non-invasive parameter has been developed by Visweswaram *et al*, [147] for screening of drugs that may protect against CCl_4 induced hepatotoxicity in rats. In these rats, urinary excretion of ascorbic acid is reduced. Measurement of urinary excretion of ascorbic acid thus serves as a parameter for hepatoprotective effect of a drug.

Hepatoprotective effects of other medicinal plants that have been evaluated in various models of liver diseases are given in Table 1.

12.3. Pancreato-protectives

The protective effect of *Emblica officinalis* in experimentally induced acute necrotising pancreatitis in dogs has been evaluated by Thorat *et al*, [148]. *Emblica officinalis* inhibited the increase in serum amylase caused by pancreatitis. Microscopical examination showed that the acinar cell damage and total inflammatory score was significantly less in dogs pretreated with *Emblica officinalis*.

12.4. Myelo-protectives

Withania somnifera prevented mylosuppression induced by one or more of the following 3 compounds, cyclophosphamide, azathioprine or prednisolone, as seen by a significant increase in haemoglobin concentration, RBC and WBC counts, platelet count and body weight and hemolytic antibody responses to human erythrocytes[149].

12.5. Radio-protectives

Oral administration of Rasayana group of drugs (from Ayurveda) were found to significantly increase total WBC count, bone marrow cellularity, natural killer cell and antibody dependent cellular cytotoxicity in gamma radiation exposed mice. Rasayanas reduced radiation induced lipid peroxidation in liver[150].

Methanolic extract (75%) of *Withania somnifera* (a plant belonging to the Rasayana group of drugs) significantly increased the WBC count in normal Balb/c mice and reduced the leucopenia induced by sublethal dose of gamma radiation. It also increased bone marrow cellularity and normalised the ratio of normochromatic to polychromatic erythrocytes following radiation. *Withania somnifera* probably exerts its effects by stimulating stem cell proliferation[151].

Active principles of *Withania somnifera* consisting of equimolar concentrations of sitoindosides VII-X and withaferin A induced a dose-related increase in superoxide dismutase, catalase and glutathione peroxide activities in rat brain frontal cortex and striatum, comparable to deprenyl, a known antioxidant[152].

Oral administration of anti-oxidants *viz*. curcumin, ellagic acid, bixin and alpha-tocopherol significantly decreased lung collagen hydroxyproline and thus lung fibrosis in rats following whole body irradiation. They also lowered serum and liver lipid peroxidation and liver superoxide dismutase activity and increased catalase activity. They also decreased the frequency of micronucleated polychromatic erythrocytes seen after whole body irradiation in mice[153].

The water extract of leaf of *Ocimum santum* was more effective and less toxic, as compared to aqueous ethanol extract, in improving the survival rate in mice, when administered intra-peritoneally before a whole body exposure to 11Gy of 60 Co gamma radiation. The intra-peritoneal route gave the best protection as compared to intra-muscular, intra-venous or oral routes[154].

12.6. Oculo-protectives

Leaves of *Ocimum sanctum* delayed the onset as well as the subsequent maturation of cataract significantly in 2 models of cataract *i.e.* galactosamic cataract in rats and naphthalene cataract in rabbits[155].

12.7. Membrane stabilizers

The leaf and root extracts of *Vernonia lasiopus* and *Vernonia galamensis* demonstrated prominent *in vitro* membrane stabilising property as determined by the percentage inhibition of RBC lysis [27].

13. Plants protecting against oxidative stress

13.1. UV light induced

Sobatum, purified from the plant *Solanum trilobatum* (Alarka) showed significant protection *in vitro* against UV light induced damage by free radicals on the bacteria *Salmonella typhimurium*. Similarly, it also protected against superoxide production that was generated by the reaction of photoreduced riboflavin and oxygen[156].

13.2. Cumene hydroperoxide induced

Tamra-bhasma, an organo-mineral compound from

Ayurveda, showed significant protection against cumene hydroperoxide induced lipid peroxidation and lowered reduced glutathione and superoxide dismutase levels in rat liver homogenate. It also significantly reduced malondealdehyde (MDA) levels. No alterations in biochemical and histopathological parameters was noted. The results thus suggested that tamra bhasma is a potent anti-oxidant drug and can be used in the management of lipid peroxidation[157].

Similarly, Sandhika, an Ayurvedic drug was evaluated *in vitro* using the same model (cumene hydroperoxide) and showed significant antioxidant activity[46].

13.3. Iron induced

Anti-peroxidative property of *Nardostachys jatamanasi* (Jatamanasi) was tested *in vitro* by using iron induced lipid peroxidation in rat liver homogenate. The degree of peroxidation was quantitated by thiobarbituric acid reactive substance (TBARS) content. Both the hexane and alcoholic extracts provided protection against lipid peroxidation (the hexane fraction was more potent) suggesting that the plant does have anti-oxidant activity[158].

Rubiadin, a dihydroxy anthraquinone, isolated from alcoholic extract of *Rubia cordifolia* (manjistha) demonstrated significant anti-oxidant property as it prevented lipid peroxidation induced by $FeSO_4$ and t-butylhydroperoxide (t-BHP) in a dose dependent manner. The percent inhibition was more in the case of Fe^{2+} induced lipid peroxidation. The anti-oxidant property of the preparation has been found to be better than that of EDTA, mannitol, Vitamin E and p-benzoquinone[159].

The potential of *Bacopa monniera* as an antioxidant was studied by Tripathi *et al*, [160]. The effect of the alcoholic and hexane fractions of *Bacopa monniera* on $FeSO_4$ and cumene hydroperoxide induced lipid peroxidation was studied. The alcoholic fraction showed greater protection against both that inducers and the results were comparable to known antioxidants like vitamin C. Probable mechanism of action could be through metal chelation at the initiation level and also as a chain breaker suggesting that *Bacopa monniera* is a potent anti-oxidant. The responses with *Bacopa monniera* were found to be dose-dependent. At low doses, it only slightly protected the auto-oxidation and $FeSO_4$ induced oxidation of reduced glutathione, but at higher concentrations, it enhanced the rate of oxidation.

14. Chemotherapeutic plant products

Plants which have shown anti-microbial, anti-fungal, anti-viral, anti-protozoal and anti-helminthic effects have been described in this section. Standard assays have been used by various investigators and most of the work has carried out *in vitro*.

14.1. Anti-microbial agents :

Clausenol, a carbazole alkaloid, isolated from an alcoholic extract of the stem bark of *Clausena anisata* was found to be active against gram positive and gram negative bacteria and fungi[161].

Substantial anti-microbial, anti-fungal and moderate insecticidal, sporicidal and cytotoxic activities were observed with the hexane extract of the stem bark of *Amona glabra*. Chromatographic fractionation of the stem led to the isolation of kaur-16-en-19-oic acid, which was found to be largely responsible for the biological activities observed[162].

The alcoholic extract of dry nuts of *Semecarpus anacardium* (Bhallatak) showed bactericidal activity *in vitro* against 3 gram negative strains (*Escherichia coli, Salmonella typhi and Proteus vulgaris*) and 2 gram positive strains (*Staphylococcus aureus and Corynebacterium diphtheriae*). Subsequent studies have shown that the alcoholic extracts of different parts of the plant (leaves, twigs, green fruit) also possess anti-bacterial properties, especially the leaf extract. No dermatoxic effect (irritant property) was observed in the mouse skin irritant assay[163].

No anti-bacterial activity with any extract of either the root or seeds of *Pongamia pinnata* was noted[3,4].

The acetone and alcoholic extracts of the leaves of *Cassia alata* showed significant *in vitro* anti-bacterial activity against *Staphylococcus aureus*, coagulase positive *Staphylococcus aureus, Bacillus subtilis, Bacillus cereus, Bacillus stearothermophilus, Escherichia coli, Salmonella typhi and Salmonella. dysentriae*. In addition, the alcoholic extract also inhibited growth of *Klebsiella pneumoniae* whereas the acetone extract inhibited the growth of Vibrio cholerae[164].

Due to a lack of ideal diffusion and evaporation from the surface it is generally difficult to assess the

anti-bacterial properties of aromatic oils derived from plants using the agar cup and disc diffusion methods. Hence, Agnihotri and Vaidya [165] have to developed a novel approach to study the anti-bacterial property of certain plants like *Eugenia caryophyllus, Thymus vulgaris, Cinnamonum zeylanium and Cuminum cyminum*. Volatile components of the hexane extracts of these plants were tested against standard gram positive and gram negative bacteria grown on agar slants and the results were expressed as percentage inhibition of the area of the slants. Of the 4 plants selected, *Thymus vulgaris* had the most prominent anti-bacterial activity.

14.2. Anti-fungal agents

The ethanolic extract of *Azadirachta indica* leaves demonstrated much more significant anti-dermatophytic activity as compared to the aqueous extract, when tested *in vitro* against 88 clinical isolates of dermatophytes using the agar dilution technique. The MIC90 of ethanolic extract was 100 µg/ml whereas that of aqueous extract was 500 µg/ml[166].

Four Siddha drugs *viz Nandhi mezhugh, Parangi pattai choornam, Erasa kenthi mezhugu* and *Vaan mezhugu* (in order of efficacy) were found to have significant anti-fungal activity when tested against 14 strains of *Candida albicans*[167].

Essential oil obtained from the herb of *Santolina chamaecyparissus* showed significant anti-fungal activity both *in vitro* (against 13 strains of *Candida albicans*) and *in vivo* (experimentally induced vaginal and systemic candidiasis in mice)[168]. It also showed activity against experimentally induced superficial cutaneous mycoses in guinea pigs by the hair root invasion test[169]. Anti-bacterial activity was also observed as seen by its inhibitory effects on the growth of *Staphylococcus aureus, Bacillus subtitis, Bacillus caerus* and *Escherichia coli*.

Rai [170] screened 17-medicinal plants against the test pathogen, *Pestalotiopsis mangiferae* and the results revealed that 14 plants had anti-mycotic activity whereas 3-plants, *viz*., *Argemone mexicana, Caesalpinia bonducella* and *Casia fistula* accelerated the growth of the pathogen. Maximum antimycotic activity was shown by *Eucalyptus globulus* (88%) and *Catharanthus roseus* (88%) followed by *Ocimum sanctum* (85.50%), *Azadirachta indica* (84.66%), *Ricinus communis* (Erand) (75%) and *Lawsonia inermis* (74.33%) while the minimum activity was exhibited by *Jatropha curcas* (10%).

The essential oil isolated from the leaves of *Aegle marmelos* exhibited significant anti-fungal activity against different fungal isolates and 100% inhibition of spore germination of all the tested fungi when evaluated using the spore germination assay. Kinetic studies showed that the inhibition was both concentration as well as time dependent[171].

Four compounds have been isolated from an extract prepared from the fruit rind of *Terminalia belerica viz*. termilignan, thannilignan (both lignans), 7-hydroxy-3',4'-(methylenedioxy) flavone and anolignan B. All possessed demonstrable anti-HIV-1, anti-malarial, and anti-fungal activity *in vitro* [172,173].

The natural xanthones isolated from the fruit hulls of *Garcinia mangostana* showed good inhibitory activity against the three phytopathogenic fungi, *Fusarium vasinfectum, Alternaria tenuis*, and *Dreschlera oryzae*. Substitution in the A and C rings in the derivatives of mangostin obtained by has been shown to modify the bioactivities of the compounds[174].

The petroleum ether, chloroform, acetone and ethanol (95%) extracts of the leaves of *Cassia alata* also showed significant *in vitro* anti-fungal activity against various fungi *viz*. *Aspergillus niger, R. japonicum, Candida albicans, C. tropiathis and R. glutinis*[175].

The root of *Withania somnifera* was found to be effective in prolonging the survival of Balb/c mice infected intravenously with *Apergillus fumigatus*. This protective activity is probably due to the observed increase in phagocytosis and intracellular killing capacity of peritoneal macrophages induced by treatment with *Withania somnifera*, thus suggesting that the plant has the potential to activate macrophage function in infectious states[176].

14.3. Anti-viral agents

Although initial studies by Thyagarajan *et al*, [177] with *Phyllanthus amarus* showed promising results in Hepatitis B carriers, further studies have demonstrated that the plant does not clear the hepatitis B surface antigen (HbsAg) in asymptomatic carriers of the antigen[178]. However, recently, in an *in vitro* study, the aqueous extract of *Phyllanthus amarus* was

Table 1. Illustrates the other plants that have been evaluated in various models of liver diseases and the parameters selected for their evaluation.

Plants/Plant derived agents (Author)	Damaging agent (Animals)	Parameters of evaluation
Methanolic extracts of the seeds of *Apium graveolens* Linn. and *Hygrophilia auriculata* H [268]	Paracetamol)) rats Thioacetamide)	Liver function tests (AST, ALT, alkaline phosphatase, sorbitol dehydrogenase, glutamate dehydrogenase and bilirubin), Hepatic triglycerides, Histopathology.
50% alcoholic extract of *Phyllanthus emblica* and its isolate, quercetin[269]	Country made liquor ingestion (rats). Paracetamol (mice)	Liver function tests, Histopathology.
Garlic oils[270]	Radiocalcium (mice)	Hepatic total lipids, triglycerides, phospholipids, free fatty acids
Swertia chirata[271]	CCl_4 (rats)	Liver function tests, Liver glycogen content, Serum cholesterol, Histopathology.
Ethyl acetate extract of *Acacia catechu* (katha) [272]	CCl_4 (rats)	Liver function tests, Histopathology.
Leaf extract of *Glycosmis pentaphylla*[273]	CCl_4 (rats)	Liver function tests, Histopathology.
Propolis, a natural resin produced by honey bees, rich in flavonoids[274]	Alcohol and CCl_4 (rats)	Liver function tests (AST, ALT), Blood and hepatic glutathione levels, Hepatic lipid peroxide content, Histopathology.
Powdered roots and aerial parts of *Sida rhombifolia* and their aque us extracts[41]	CCl_4, paracetamol and rifampicin (rats)	Liver function tests
Plant leaf suspension and methanolic extract of *Trichopus zeylanicus*[275]	Paracetamol (rats)	Liver function tests, Histopathology, Hepatic and lipid peroxide contents.
Methanolic extract of *Trichopus zeylanicus* [275]	Normal rats	Cholerectic activity

incubated with the Alexandar cell line, a human hepatocellular carcinoma derived cell line which has the property of secreting the Hepatitis B surface antigen (HbsAg) in the supernatant. The results demonstrated that *Phyllanthus amarus* was effective in inhibiting the secretion of HbsAg for 48 hrs thus proving its anti-hepatitis B virus property at the cellular level[179].

Glycyrrhizin, a triterpenoid glycoside obtained from *Glycyrrhiza glabra* (Yasthimadhu) was tested against RNA viruses like the Chandripura virus, Measles virus, Polio vaccine viruses type 1, 2 and 3, Polio wild type viruses 1, 2 and 3 as well as DNA viruses like the Herpes type 1 and 2 viruses *in vitro*. It inhibited the DNA virus plaque formation at lower concentrations (0.608 mM) while the RNA viruses were inhibited at higher concentrations (1.216 mM) [180].

Premanathan *et al*, [181] carried out *in vitro* screening

of mangrove plant extracts for anti-immunodeficiency virus activity. HIV infected MT-4 cells were incubated with the extract and anti-viral activity was detected using tetrazolium-based colorimetric assay. Seven extracts were found to be effective five of which (bark of *Rhizophora mucronata* and leaves of *Excoecaria agallocha*, *Ceriops decandra*, *Rhizophora apiculata*, *Rhizophora lamarckii*) completely inhibited the virus adsorption to the cells.

14.4. Anti-protozoal agents

14.4.1. Antimalarial :

Ethanolic and petroleum extracts of *Artemisia japonica, Artemisia maritimia* and *Artemisia nilegarica* were tested for anti-malarial activity, both *in vivo* and *in vitro*. *In vivo* studies were carried out in Balb/c mice using the Rane test wherein all the compounds prolonged the survival time of the mice. *In vitro*, all 3 compounds inhibited schizont maturation in chloroquine sensitive strains of *Plasmodium falciparum*[182].

Ball shaped wood scrappings soaked in 5% Neem oil (*Azadirachta indica*) diluted in acetone and placed in water storage overhead tanks controlled the breeding of *Anopheles stephensi* and *Aedes aegypti* in 45 days[183]. Similarly, application of a cream of *Azadirachta indica* on exposed body parts at the rate of 2.0 gm/person significantly protected against Aedes, Culex and Anopheles musquitoe bites[184].

14.4.2. Anti-leishmanial :

The methanolic extract of *Swertia chirata* was found to inhibit the catalytic activity of topoisomerase I enzyme of *Leishmania donovani*. On subjecting the extract to fractionation, it yielded 3 secoiridoid glycosides, amarogentin, amaroswerin and sweroside of which amacogentin was found to be a potent inhibitor of topoisomerase I and exerted its effect by interacting with the enzyme, thus preventing binary complex formation[185].

14.4.3. Anti-trypanosomial

Crude 50% ethanolic extract of *Parthenium hysterophorus* flowers exhibited trypanocidal activity against *Trypanosoma evansi* both *in vitro* and *in vivo*. Toxicity was seen only at 1g / kg dose[186].

14.5. Anthelminthic agents

14.5.1. Anti-Nematodes

Kumar *et al* [187] has studied the mechanism of action of palasonin, the active principle of *Butea frondosa* seeds on *Ascaridia galli*. Palasonin inhibited glucose uptake and depleted the glycogen content[187] and thus the possible mechanism of its anthelminthic action may be related to inhibition of energy metabolism.

Both aqueous and alcoholic extracts of the leaves of *Sencio nudicaulis* Buch Ham were found to exert anti-filarial activity when tested against *Setaria cervi* (Nematoda Filarioidea). The effective concentrations differed for the aqueous and alcoholic extracts suggesting the presence of a cuticular permeability barrier. Both extracts also demonstrated micro-filaricidal action *in vitro*. Their anti-filarial responses were similar to diethylcarbamazine in that they too did not block the stimulant effect of acetylcholine on the worm[188].

Co-administration of Regulipid, a herbal formulation, with diethylcarbamazine therapy to patients suffering from filariasis was found to decrease chyluria in these patients[189].

Mustafa *et al* [190] injected the excretory-secretory products released by the adult *Setaria cervi*, a bovine filarial parasite, into rabbits to raise polyvalent antibodies. These antibodies can be used to detect circulating antigens in sera by counter immuno-electrophoresis and serve as a diagnostic test for filariasis.

14.5.2. Anti-Trematode (fluke)

The root tuber extract of *Flemingia vestita*, an indigenous medicinal plant in Meghalaya, exhibited anti-helminthic activity *in vitro*, against 2 species of flukes, *Artyfechinostomum sufrartyfex* and *Fasciolopsis buski*. It caused paralysis in both the species. Stereoscanning observations on the tegumental surfaces revealed sloughing off of most of the spines or their deformation and wrinkling and rupture of the general tegument[191].

14.5.3. Agents with molluscicidal activity

The leaf, bark, cake and oil of *Azadirachta indica* and synthetic pesticides derived from the plant demonstrated both, dose and time dependent, molluscicidal activity when tested against the snails, *Lymnaea*

acuminata and Indoplanorbis exustus. The cidal effect of pure azadirachtin was greater then that of the synthetic molluscicides[192].

15. Anti-mutagenic plants

Punark, a mixture of solvent extracts of natural products, namely turmeric (*Curcuma longa*), betel leaf (*Piper betel*) and catechu (*Acacia catechu*) protected against benzo (a) pyrene induced chromosomal damage in human lymphocytes *in vitro* [193]. Alcoholic extracts of tumeric oil (TD) and tumeric oleoresin (TOR) showed anti-mutagenic effect *in vitro*. They also demonstrated chemoprotective effect in lymphocytes of normal healthy subjects *in vitro* when tested against benzo (a) pyrene induced DNA damage. *In vivo* the extracts reduced DNA damage (cytogenetic damage) in oral mucosal cells of patients with oral submucous fibrosis[194].

Water, oil and alcoholic extracts of nuts of *Semecarpus anacardium* were found to be anti-mutagenic when tested against benzo (a) pyrene (BZP) in the bacterial test system using *Salmonella typhimurium* strains TA98 and TA100. The water extract was less effective as compared to the oil and alcoholic extracts. In addition, the water and alcoholic extracts showed anti-mutaginic effect when tested in lymphocyte cultures of normal healthy volunteers[195].

Ellagic acid, a fraction isolated from *Terminalia arjuna* has been evaluated for it anti-mutagenic potential in TA98 and TA100 strains of *Salmonella typhimurium* against direct and indirect - acting mutagens. The fraction was quite effective against S9-dependent 2AF while it showed moderate effect against NPD[196].

16. Anti-cancer plants

The potential role of various plants in cancer therapy as either a direct anti-cancer agent, chemopreventive agent, radiosensitizer or immunity enhancer is presented in the following paragraphs.

Evaluation of the *in vitro* anti-cancer effects of bioflavonoids, *viz*. quercelon, catechin, luteolin and rutin against human carcinoma of larynx (Hep-2) and sarcoma 180 (S-180) cell lines showed that only luteolin and quercetin inhibited the proliferation of the cells. Luteolin caused depletion of glutathione in the cells and a decline in DNA synthesis, as seen by ^{3}H thymidine uptake studies, thus demonstrating its anti-cancer potential[197].

The anti-tumor effect of the crude extract of *Centella asiatica* as well as its partially purified fraction was studied in both, *in vitro* short and long term chemosensitivity test systems and *in vivo* tumor models. The purified fraction inhibited the proliferation of transformed cell lines of Ehrlich ascites tumor cells and Dalton's lymphoma ascites tumor cells more significantly than the crude extract. It also significantly suppressed the multiplication of mouse lung fibroblast cells in long term culture. *In vivo* administration of both extracts retarded the development of solid and ascites tumors and increased the lifespan of the tumor bearing mice. Tritiated thymidine, uridine and leucine incorporation assays suggest that the purified fraction acts directly on DNA synthesis[198].

The methanol eluted fraction of the petroleum ether extract of the root bark of *Salacia oblonga* Wall showed 100% cytotoxicity on Ehrlich ascites tumor cells[86].

Fresh root suspension of *Janakia arayalpathra* exhibited strong anti-tumor effects in mice challenged with Ehrlich Ascitic Carcinoma (EAC) cells. It prolonged the survival of all mice and protected a number of mice from tumor growth, probably by enhancing the activity of the immune system[199].

Withaferin A, a steroidal lactone isolated from the roots of *Withania somnifera*, reduced survival of V79 cells in a dose-dependent manner. The applicability of this drug as a radiosensitizer in cancer therapy needs to be explored[200].

Banerjee *et al*, [201] have studied the modulatory influence of the alcoholic extract of leaves of *Ocimum sanctum* on various enzyme levels in the liver, lung and stomach of mouse. Oral treatment with the extract significantly elevated the activities of cytochrome P450, cytochrome b5, arylhydrocarbon hydroxylase and glutathione S-transferase enzymes, all of which are important in the detoxification of carcinogens as well as mutagens. Moreover, it also significantly elevated extra-hepatic glutathione S-transferase and reduced glutathione levels in the liver, lung and stomach. These observations suggest that the leaf extract or its active principles may have a potential role in the chemoprevention of chemical carcinogenesis.

Studies conducted by Rao *et al*, [202] have shown that pergularinine (PgL) and tylophorinidine (TPD) isolated from *Pergularia pallida* are potently toxic and inhibit the growth of *Lactobacillus leichmannii* cells by binding to thymidylate synthetase. The binding led to significant inhibition of thymidylate synthetase activity making them potential anti-tumor agents.

Petroleum ether extract of *Hygrophilic spinosa* exhibited anti-tumor activity in Ehlrich ascitic carcinoma and sarcoma 180 bearing mice [203].

Aqueous extract of *Podophyllum hexandrum*, a herb from the Himalayas, demonstrated significant anti-tumor effects when drug was tested in strain 'A' mice carrying solid tumors developed by transplanting Ehrlich ascites tumor cells. Radioprotective effects were also seen when the drug was administrated to mice before whole body lethal irradiation of 10 Gy[204].

The chemopreventive efficacy of *Trianthema portulacastrum* L.Aizoaceae was tested in male Sprague-Dawley rats. Hepatocarcinogenesis was induced by the potent carcinogen diethylnitrosoamine (DENA). Treatment of the rats with aqueous, ethanolic and chloroform fractions of the plant extract at a dose of 100 mg/kg once daily reduced the incidence, numerical preponderance, multiplicity and size distribution of visible neoplastic nodules. Morphometric evaluation of focal lesions showed a reduction in number of altered liver cell foci per square centimeter as well as of average area of individual lesion. A decrease in the percentage of liver parenchyma occupied by foci seems to suggest the anti-carcinogenic potential of the plant extract in DENA-induced hepatocarcinogenesis[205].

Pretreatment with *Ocimum sanctum* leaf extract followed by the addition of 7,12-dimethylbenz[a]anthracene (DMBA) significantly blocked the formation of DMBA-DNA adducts in primary cultures of rat hepatocytes *in vitro*. The viability of the cells was not adversely affected by the extract[206].

17. Immune active plants

Modulation of the immune response through stimulation or suppression may help in maintaining a disease free state. Agents that activate host defence mechanisms in the presence of an impaired immune responsiveness can provide supportive therapy to conventional chemotherapy. Upadhyay[207] has highlighted the therapeutic potential of immunomodulatory angets from plant products. They have evaluated Indian medicinal plants for immunomodulatory activity[208]. The authors have also reviewed the Ayurvedic concepts of preventive health care. A list of Ayurvedic medicinal plants showing immunomodulatory activity has been provided which includes agents like *Withania somnifera, Allium sativum, Azadirachta indica, Piper longum, Asparagus racemosus, Glycyrrhiza glabra, Aloe vera, Gmelina arborea* and *Tinospora cordifolia.*

Thatte and Dahanukar, [209] have described how clues from the description of ancient writings can lead to the development of new immunostimulatory agents. The experiments carried out to prove the rasayana concept of Ayurveda have demonstrated that *Asparagus racemosus, Tinospora cordifolia* and *Withania somnifera* protected animals against infections in normal and immunosuppressed states induced by hemisplenectomy or surgery[210]. These plants also produced leucocytosis with predominant neutrophilia and prevented, to varying degrees, the leucopenia induced by cyclophosphomide. They were found to activate the polymorphonuclear and monocyte-macrophage systems. Only those rasayanas which produced sweet (madhur) vipaka (*Tinospora cordifolia, Asparagus racemosus, Emblica officinalis, Terminalia chebula and Withania somnifera*) were found to stimulate the reticulo-endothelial system, but not those like *Acorus calamus, Commiphora mukul* and *Picorrhiza kurroa*, which produced bitter (katu) vipaka[210].

Among the immunostimulant rasayanas, *Tinospora cordifolia* has been extensively studied by Dahanukar *et al* [211]. It has been found to activate the mononuclear cells to release cytokines like GMCSF [212] and IL-1 in a dose dependent manner [210]. Whole aqueous extract of *Tinospora cordifolia*, standardized using HPTLC, has been evaluated as an adjuvant in clinical conditions like obstructive jaundice, tuberculosis and cancer chemotherapy and has been found to increase the efficacy of conventional therapy[210]. Active principles of *Tinospora cordifolia* were found to possess anticomplementary and immunomodulatory activities. Syringin (TC-4) and cordiol (TC-7) inhibited the *in vitro* immunohaemolysis of antibody - coated sheep erythrocytes by guinea pig serum by inhibiting the C3-convertase of the classical

complement pathway. The compounds also gave rise to significant increases in IgG antibodies in serum. Both humoral and cell-mediated immunity were dose-dependently enhanced. Macrophage activation was reported for cordioside (TC-2), cordiofolioside A (TC-5) and cordiol (TC-7) and this activation was more pronounced with increasing incubation times[213].

The effect of *Asparagus racemosus, Tinospora cordifolia, Withania somnifera* and *Picorrhiza kurroa* on macrophage function obtained from mice treated with the carcinogen, ochratoxin (OTA) was evaluated by Dhuley[214]. Treatment with these plants significantly attenuated the OTA-induced suppression of chemotactic activity as well as IL-1 and TNF-α production by macrophages. Moreover, *Withania somnifera* potentiated macrophage chemotaxis and *Asparagus racemosus* induced excessive production of TNF-α as compared to controls.

Ray *et al* [215] demonstrated that ovalbumin immunized mice treated with *Azadirachta indica* leaf extract had higher IgG and IgM levels and anti-ovalbumin antibody titres as compared to control (humoral response). *Azadirachta indica* also induced cell mediated response as seen from the enhancement of macrophage migration inhibition and footpad thickness. These findings were supported by Ansari *et al*, [216]. They found that *Azadirachta indica* potentiated the antibody titres following typhoid H. antigen immunisation and induced delayed hypersensitivity following administration of tuberculin and DNCB to animals. In human volunteers, it stimulated humoral immunity by increasing antibody levels and cell mediated immunity by increasing total lymphocyte and T-cell count in 21 days.

Oral pretreatment with leaf extract of *Azadirachta indica* reversed the inhibitory effect of restraint stress on formation of anti-sheep RBC antibody titres in rats immunized with sheep RBC and also the increase in foot pad thickness. It reversed the DDT induced suppression of antibody response and leucocyte migration inhibition in tetanus toxoid immunized rats. Restraint stress along with administration of DDT in subthreshold doses resulted in an inhibition of the immune response. *Azadirachta indica* attenuated the immunotoxicity of environmental and xenobiotic stressors[217].

Root suspension of *Janakia arayalpathra* was found to have immunostimulatory properties in mice. It stimulated an increase in humoral antibody titres and also of antibody secreting spleen cells in the plaque forming cells assay following immunisation with sheep erythrocytes. It also increased the number of peritoneal macrophages and produced an increase in delayed hypersensitivity reaction in mice [199].

The alkaloidal fraction of *Boerrhiva diffusa* significantly restored the suppressed humoral response in stressed rats as observed by Mungantiwar *et al*,[218] wherein *Boerrhiva diffusa* increased the suppressed antibody titres following immunization by sheep RBCs in rats subjected to restraint stress. It also significantly reversed the depleted adrenal cortisol level and the elevated plasma cortisol level in the stressed rats, thus appearing to have a corticosteroid sparing effect in experimental stress.

Immune-21, a polyherbal natural product, has been shown to exhibit significant immunopotentiating and immuno-prophylactic activity, both *in vitro* and *in vivo*[219].

18. Adaptogens

Adaptogen is a term used to describe agents that increase the nonspecific resistance of organisms against a variety of stressors. A recent review on adaptogens, [211] describes the developments taking place in this field and the problems associated in the evaluation of adaptogens.

In a series of experiments the whole, aqueous standardised extracts of *Tinospora cordifolia, Asparagus racemosus, Emblica officinalis, Withania somnifera, Piper longum* and *Terminalia chebula*, were administered orally to experimental animals, in a dose extrapolated from the human dose. These animals were exposed to a variety of biological, physical and chemical stressors. The plants were found to offer protection against these stressors[211]. All the plants reversed the effects of cisplatin on gastric emptying, while *Tinospora cordifolia* and *Asparagus racemosus* also normalised cisplatin induced intestinal hyper-motility, complying to the definition of an adaptogen. They were found to be safe in both acute and subacute toxicity studies. All of them produced immunostimulation[211]. The type of extract (methanolic extract of *Withania somnifera* was more active) and time of administration (the best effects were observed only if

given as pre-treatment) also influenced the effects. Of these plants *Emblica officinalis* strengthened the defense mechanisms against free radical damage induced during stress. The effect of *Emblica officinalis* appeared to depend on the ability of target tissues to synthesize prostaglandins. On the other hand, gastroprotective effect of *Tinospora cordifolia* was probably mediated through a predominantly immunostimulant mechanism as the protection was found to disappear on blocking the macrophage function.

In normal mice, high doses of *Tinospora cordifolia* significantly increased apoptosis in bone marrow cells. The therapeutic doses (100-200 mg/kg) were devoid of such effect. However, at the same therapeutic doses, it induced apoptosis in malignant cells, but protected the normal bone marrow from apoptosis induced by cyclophosphamide. This variable effect of Tinospora cordifolia (of increasing or decreasing apoptosis) depending on the stressor (either cancer or cyclophosphamide) as well as the cell type (S-180 or bone marrow cells) suggests its true potential as an adaptogen. It is of further interest to note that *Tinospora cordifolia* increases the bone marrow proliferative fractions at 100 and 200 mg/kg doses thus leading to leucocytosis. If the dose is increased, apoptosis is observed and the leucocytosis is blunted. This apparent paradox may be due to its effects on c-myc, a gene that causes both proliferation as well as induces apoptosis depending on the environment. It is exciting thus to hypothesise that *Tinospora cordifolia* may be producing some of its effects via activation of c-myc and inducing 'genotypic' adaptation.

Ocimum sanctum, known to have antistress properties, was recently studied by Sembulingam *et al*, [220] for its antistress effects against a different type of stress *i.e.* noise pollution, in rats. The ethanolic extract of *Ocimum sanctum* reversed the changes in plasma levels of corticosterone induced by exposure to both acute and chronic noise stress, indicating the antistress property of the plant against noise.

Studies have been reported in the literature to explore the possible mechanisms responsible for adaptogenic effect. For example, *Panax ginseng* did not modify brain and hypothalamic 5HT levels in unstressed rats, however, it attenuated restraint stress induced elevation of 5HT levels[221].

19. Nutraceutics

This is an emerging field of therapy. As we come to the end of this millennium, more and more people are getting health conscious and are looking at dietary substances for preventive or curative effects. Support towards this line of thinking from the scientific field is described in the following paragraphs.

19.1. Indian spinach (Beta vulgaris)

Dietary consumption of green vegetables has been associated with protection against mutagenic and clastogenic activity of genotoxicants. Chlorophyll, present in all green plants, has been suggested to be the principal factor involved. Sarkar *et al*, [222] compared the clastogenic or anticlastogenic effects of crude aqueous extract of leaf of Indian spinach, (*Beta vulgaris* L. var. benghalensis Hort.) and equivalent amounts of chlorophyll extracted from leaf, purified chlorophyll and chlorophyllin (a sodium copper derivative). After treatment for 7 days, the mice were administered potassium dichromate, a known metallic clastogen and sacrificed 24 hrs later. Cytogenetic end points were chromosomal aberrations and damaged cells. Results showed that both crude leaf extract and chlorophyllin were nonclastogenic and reduced the clastogenic effects of potassium dichromate. However, chlorophyll was clastogenic. The protective effect of the crude leaf extract was attributed to the total effect of the interaction between the different components within the leaf extract, thus neutralising the clastogenic effects of chlorophyll.

19.2. Karela (Momordia charantia)

Substitution of groundnut oil with palmolein in cereal based lactovegetarian diets provides about 30% of total fat calories, doubles the saturated fatty acids and reduces by half the linoleic acid content. The hypoglycemic activity of the alcoholic extract of the pulp of *Momordia charantia* (Karela) was evaluated in 3 experimental models of diabetes. In the normal glucose primed rat model, it decreased plasma glucose that was not accompanied by increase in insulin secretion. No evidence of tachyphylaxis to its effects on repeated dosing was found. In streptozotocin induced diabetic rats, it improved glucose tolerance and significantly reduced plasma glucose. The extract also increased the rate of glycogen synthesis from ^{14}C- glucose by 4-5 fold in the liver of

normal rats. All the results suggest that the mechanism of action of *Momordia charantia* could be partly attributed to increased glucose utilisation in the liver rather than an insulin secretion effect[223].

19.3. Edible oils

Ghafoorunissa *et al*, [224] studied the effects of the substitution of palmolein oil for ground nut oil on selected cardiovascular risk factors and membrane functions in middle aged subjects. The effects were essentially similar with both treatment regimes. This study indicates that palm oil may not produce the deleterious effects associated with saturated fatty acids[225]. The author further explained that the tocols present in palm oil are natural biological anti-oxidants and can therefore augment the anti-oxidant potential of Indian diets. Also, red palm oil is the richest natural source of carotenes (especially beta-carotene) which are powerful biological anti-oxidants and hence, red palm oil can be used to prevent vitamin A deficiency which is widespread in India.

A study conducted by Kumar, [226] ruled out the association of increased incidence of coronary heart disease (CHD) with the high consumption of coconut and coconut oil in Kerala. Since their consumption of coconut and coconut oil and saturated fats and found that both groups did not differ in 32 CHD patients and 16 age and sex matched healthy controls.

19.4. Turmeric (Curcuma longa)

Curcumin (from *Curcuma longa*) protected against decrease in heart rate and blood pressure and biochemical changes in cat heart after coronary artery ligation. It also prevented the elevation of MDA content and lactate dehydrogenase release in the ischaemic zone. However, it did not prevent the increase in myeloperoxidase activity, indicating that curcumin protects against ischaemia induced changes by increasing the antioxidant defense mechanisms[227].

Deshpande *et al*, [228] demonstrated that both pre-treatment as well as concurrent treatment of turmeric extract in CCl_4 treated rats caused a reduction in cholesterol, bilirubin, SGOT, SGPT and alkaline phosphatase activity; concurrent treatment offering more significant protection.

The anti-mutagenic activity of Curcumin has already been described under the section 'Anti-mutagenic plants'.

19.5. Fenugreek (*Trigonella foenum graecum*)

Administration of unroasted and roasted powdered forms of seeds of *Trigonella foenum graecum* (fenugreek) to alloxan induced diabetic rats produced a significant fall in various serum lipids like total cholesterol, LDL and VLDL cholesterol and triglycerides in normal rats and in addition, increased HDL cholesterol in diabetic rats[229].

19.6. Curry leaf (Murraya Koenigii) and Mustard (Brassica juncea)

Whole curry leaf (*Murraya Koenigii*) and mustard (*Brassica juncea*) fed to rats at doses equal to normal human intake did not cause any adverse effect on food efficiency ratio, haematological parameters, liver and renal function tests, fibrin level and glycosylated haemoglobin. No histopathological changes were observed in the liver[230]. Both, plants showed significant hypoglycemic action in rats. There was an increase in the concentration of hepatic glycogen and glycogenesis and a decrease in glycogenolysis and gluconeogenesis [231].

The status of lipid peroxidation was investigated in rats fed *Murraya Koenigii* and *Brassica juncea*. Concentration of malondialdehyde showed a significant decrease, while hydroperoxides and conjugated dienes were significantly increased in liver and heart of both the experimental groups. Superoxide dismutase and catalase activity was found to be increased in liver and heart of both the spices administered groups. Glutathione levels in liver, heart and kidney were lowered in rats administered these species. Glutathione reductase, glutathione peroxidase and glutathione S-transferase activity showed a sharp increase in the experimental group compared to the controls[232].

19.7. Mint leaf (Mentha spicata)

Mint leaf has been shown to have significant stimulatory effect on the lipase activity of pancreas and intestinal mucosa in rats. It also stimulated intestinal amylase activity[233]. It, however, had no effect on bile secretion and its composition.

19.8. Onion (Allium cepa)

Augusti[234] in his review on the therapeutic values of onion (*Allium cepa*) and garlic (*Allium sativum*), has discussed the presence of many sulfur containing

active principles mainly in the form of cysteine derivatives in onion and garlic, that are responsible for the various biological activities such as anti-diabetic, antibiotic, hypocholesterolaemic and fibrinolytic.

19.9. Garlic (Allium sativum)

S-allyl cysteine sulfoxide, isolated from garlic (*Allium sativum*), has been shown to be as active as gugulipid in controlling hypercholestermia, obesity and derangement of enzyme activities in cholesterol diet fed rats. The beneficial effects are partly due to its inhibitory effects on transaminases, alkaline phosphatase, lipogenic enzymes and HMG CoA reductase and partly due to stimulatory effects on plasma lecithin-cholesterol acyl transferase lipolytic enzymes and fecal excretion of sterols and bile acids[235]. Further studies by these authors[236] showed that the treatment also reversed the lipid peroxidation and decrease in reduced glutathione levels, superoxide dismutase and catalase activities in cholesterol fed rats.

Garlic oil stimulated lipase activity only in the intestinal mucosa and reduced pancreatic trypsin and chymotrypsin activities. Like mint, garlic also did not show any effect on bile secretion and composition[233].

Garlic protein diet or daily administration of garlic oil to 2% cholesterol fed rats controlled significantly the increases in sulphated glycosaminoglycans in their heart and aorta. However, hyaluronic acid level increased. UDPG dehydrogenase decreased and several degrading enzymes increased in the aorta on treatment. The effects of treatment were just the reverse in liver. The high percentage of cysteine in garlic protein and the reactive disulphide group in the oil may be responsible for their beneficial effects[237].

Both garlic protein (16% of diet) and garlic oil (100 mg/kg/day) exhibited significant lipid lowering effects in rats fed with cholesterol diet. The hypolipidemic action is primarily due to a decrease in hepatic cholesterogenesis in the treated rats. Even though garlic oil was found to be more effective, the garlic protein is more palatable and free from an obnoxious smell[238].

Administration of water soluble proteins of garlic to alcohol fed rats caused a significant increase in antiperoxide activity and decrease in activity of glutathione peroxidase and gluthathione S-transferase[239].

19.10. Ginger (Zingiber officinalis)

The acetone and 50% alcoholic extracts of *Zingiber officinalis* (ginger) exhibited significant anti-emetic activity with the acetone extract being more effective than the ethanolic extract against emesis induced by 3 mg/kg cisplatin in healthy mongrel dogs[240]. These findings suggest that ginger could be an effective and cheap anti-emetic adjunct to cancer chemotherapy.

19.11. Nutmeg (Myristica fragrans)

Myristica fragrans (nutmeg) seed extract administration to hypercholesterolemic rabbits reduced both total and LDL cholesterol, lowered the cholesterol/phospholipid ratio and elevated the decreased HDL-ratio significantly. This extract also prevented the accumulation of cholesterol, phospholipids and triglycerides in liver, heart and aorta and dissolved atheromatous plaques of aorta. Fecal excretion of cholesterol and phospholipid were significantly increased in these rabbits[241].

The ethanolic extract of *Myristica fragrans* demonstrated significant hypolipidaemic effects in experimentally induced hyperlipidaemia in rabbits. It lowered the lipoprotein lipid levels, total cholesterol, LDL cholesterol and triglycerides. HDL cholesterol was not significantly affected. Total cholesterol:HDL and LDL: HDL ratios were also significantly lowered. It lowered the level of total cholesterol in the heart and liver and demonstrated platelet antiaggregatory activity[242].

19.12. Piperine (Piper nigrum and Piper longum)

Piperine, [1-[5-[1,3-benzodioxol-5-yl]-1-oxo-2,4, pentadienyl] piperidine], a pungent alkaloid present in *Piper nigrum* Linn, and *Piper longum* Linn. has been shown to enhance the bioavailability of various structurally and therapeutically diverse drugs.Data obtained from intestinal everted sacs studies suggest that piperine is absorbed very fast across the intestinal barrier through the transcellular pathway. It may act as an apolar molecule and form apolar complex with drugs and solutes. It may modulate membrane dynamics due to its easy partitioning thus helping in efficient permeability across the barriers[243].

However, in another study[244], Trikatu, a combination of *Piper longum, Piper nigrum* and *Zingiber officinalis* was found to decrease the bioavailability of isoniazid in rabbits as measured by the alteration of peak

plasma concentration (C_{max}) levels and area under curve (AUC).

19.13. Betel leaf (Piper betle)

The influence of two varieties of betel leaf (*Piper betle* Linn.) namely, the pungent Mysore and non-pungent Ambadi, was examined on digestive enzymes of pancreas and intestinal mucosa and on bile secretion in experimental rats. The results indicated that while these betel leaves do not influence bile secretion and composition, they have a significant stimulatory influence on pancreatic lipase activity. The Ambadi variety of betel leaf has a positive stimulatory influence on intestinal digestive enzymes, especially lipase, amylase and disaccharidases whereas a slight lowering in the activity of these intestinal enzymes was seen when Mysore variety of betel leaf was administered. The latter variety also had a negative effect on pancreatic amylase. Further, both the betel leaf varieties have shown decreasing influence on pancreatic trypsin and chymotrypsin activities[245].

The anti-mutagenic potential has already been described earlier in this chapter.

19.14. Mowrah (Madhuca latifolia)

Mowrah (*Madhuca latifolia*) seeds are used as animal feed as they yield 40-50% edible fat and the meal contains saponins besides protein and high level of carbohydrates. However, the seeds were found to be toxic when administered to young and adult rats at levels of 10 to 40% in diet. The animals showed marked inhibition of feed intake and loss of body weight resulting in mortalities. Histopathological examination revealed a gradation of damage from slight erosion of the tip of villi of intestinal mucous membrane to complete necrosis and destruction of it, with increasing amounts of mowrah seed meal in diets. The other significant change was a severe vacuolar degeneration of kidney tubular cells[246].

20. Phytochemistry

Following are some of the studies carried out to find out the active principle of plants.

20.1. Clausena anisata

Two new carbozole alkaloids, designated as clausenol and clausenine, were isolated from alcoholic extract of the stem bark of *Clausena anisata*. Their structures were established as 1-hydroxy-6-methoxy-3-methylcarbazole and 1,6-dimethoxy-3-methyl carbazole, respectively, from physical and chemical evidence and synthesis. Clausenol was found to be active against gram-positive and gram-negative bacteria and fungi[161].

20.2. Albizia lebbeck

Three main saponins named albiziasaponins A, B and C were isolated from the bark of *Albizia lebbeck* and their structures were established through spectral analyses. These may be responsible for the antiallergic properties of *Albizia lebbeck* [247].

20.3. Ocimum sanctum

Gas liquid chromatographic analysis of fixed oil of *Ocimum sanctum* revealed the presence of five fatty acids (stearic, palmitic, oleic, linoleic and linolenic acids) which in further studies, demonstrated significant anti-inflammatory activity[35,36].

20.4. Bacopa monniera

Chemical characterization of the plant, *Bacopa monniera* has been carried out by Garai *et al* [248,249]. Three new dammarane-type triterpenoid saponins, bacopasaponins A,B and C and a new dammarane type pseudojujubogenin glycoside, bacopa saponin D have been isolated and identified by spectroscopic methods and some chemical transformations.

20.5. Cerpegia juncea

From the chloroform extract of finely chopped, shade dried whole plant of *Cerpegia juncea* cerpegin has been derived which is the active principle responsible for its analgesic properties[30].

20.6. Ochna obtusata

Column chromatography of chloroform extract shade-dried and powdered stem bark of *Ochna obtusata* afforded an orange compound, crystallised from acetone which gave elemental analysis, IR, UV, HNMR and MS data corresponding to Prezewalskinone-B. This is probably the active principle that is responsible for the analgesic and anti-inflammatory properties of the plant[250].

20.7. Camellia sinensis

Air-dried roots of *Camellia sinensis* were extracted by percolation with methanol at ambient

temperature. Solvent extraction, chromatography and hydrolysis procedures progressively yielded 3-0-β-D-glucopyranoso-a-spinasterol. Further studies will have to be carried out to correlate these principles with the pharmacological (hypoglycaemic and ulceroprotective) activities of the plant[251].

20.8. Phytolectins

Lectins are structurally diverse, carbohydrate binding proteins that bind reversibly to specific mono-or oligosaccharides. They are being used by the biomedical scientists and biochemists in blood typing and stimulation of cell for chromosome analysis and gene mapping, in cell separation, identification of complex glycoproteins and typing bacteria. Cell targeting by lectins in cancer therapy is still in its infancy. Sengupta *et al*, [252] have reviewed the potential of these biomolecules in medicine.

Lectin activities in roots, nodules, stems and leaves of 1-6 week old peanut plant (*A.hypogaea*) were checked by erythrocyte (human and rabbit) agglutination and sugar inhibition assays. Human and rabbit erythrocyte agglutinating activities were specifically inhibited by lactose/cellobiose (SLII) and methyl alpha-mannoside (SLI) respectively. Seed embryos and cotyledons agglutinated neuraminidase treated human erythrocytes and that activity was inhibited by T-disaccharide. In the roots of field grown plants SLI was the major activity, while nodules showed both activities (SLI and SLII). Specific activities of SLI and SLII were maximal in stem tissue and minimal hypocotyl. Actively growing tissues contained more SLII activity in comparison to the mature tissues. Immunological tests indicated that all the vegetative tissue lectins are serologically related[253].

21. Miscellaneous

21.1. Reviews on medicinal plants

It is beyond the scope of this chapter to justify review articles that have been published in the last 5 years. For the benefit of the readers, the articles are summarised in the following paragraphs. An interested reader may refer to them for detailed information.

Suresh, *et al*, [254] have investigated the phytochemical and pharmacological activities of 25 medicinal plants, commonly used by the tribals of Nilgiris, using various experimental models *viz.,* CNS-active plants (*Araucaria bidwilli, Brachylepsis nervosa*), plants with analgesic activity (*Araucaria bidwilli, Brynopsis lacinosa, Cyclea peltata, Ipomoea obscura, Mirabilis jalappa, Santolina chamaeccyparissus, Stephania japonica*), anti-inflammatory plants (*A. houstanianum, Araucana bidwilli, Bauhinia variegate, Iberis amara, Ipomoea obscura, Mirabilis jalappa, Santolina chamoeccyparissus,Stephania japonica, Thunbergia fragrans*), antipyretic plants (*Araucaria bidwilli, Malvastrum coromandelianum, Rumex nepalensis, Santolena chamaeccyparissus, Stephamia japonicum,Toddalia asiatica*), plants with local anaesthetic activity (*Mirabilis jalappa*), plants affecting smooth muscle (relaxant effect) (*Araucaria bidwilli, Bauhinia variegata, Brachylepsis nervosa, Calotropis gigantea, Cardiospermum helicacabum, Impomea obscura, Malvastrum coromandelianum, Melianthus major, Rubia cordifolia, Stephania japonica, Thunbergia fragrans*), chemotherapeutic agents (Brachylepsis nervosa, Calotropis gigantea, Ipomoea obscura), plants modulating fertility (*Ailanthus excelsea*), CVS active plants (*Cystisus scoparius, Cystisus scoparius*), diuretic plants (*Cystisus scoparius, Sida cordifolia, Toddalia asiatica*), ulceroprotectives (*Araucaria bidwilli, Malvastrum coromandelianum, Santolina chamaeccyparissus*), anti-diarrhoeal plants (*Bauhinia variegata, Ipomoea obscura, Malothria perpusilla, Thunbergia fragrans*), haemostatic plants (*A houstanianum, Toddalia asiatica*) and effect on biochemical parameters (*Amarantus spinosus*).

Bhandary, *et al*, [255] conducted ethnomedical field study on 98 medicinal preparations, involving 69 species of plants, used by the Siddis of Uttara Kannada in the state of Karnataka. Their findings include 40 hitherto unknown medicinal uses of known medicinal plants. Among these, the use of the stem sap of *Calamus thwaitesii* as an antifertility drug, and the use of the flowers of *Ichnocarpus frutescens* and the rhizome of *Hedychium coronarium* in the treatment of diabetes are noteworthy. Aswal *et al*, [256] have described the results of their scientific endeavours in which the alcoholic extracts of 266 botanically identified plant materials from 222 plant species were tested for various biological activities including chemotherapeutic and pharmacological. Eighty-nine extracts were shown to possess biological activity. Follow-up studies have been carried out on some of these plants with confirmed activity. The active

principles and results of these studies have also been discussed. The chemistry, pharmacology and traditional medicinal uses of various Vernonia species, also called as sahadevi, (*viz. Vernonia cinerea, Vernonia anthehelmintica, Vernonia amygdalina, Vernonia lasopius* etc.) have been reviewed by Johri and Singh[257]. Pharmacoepidemiological survey carried out by Karandikar *et al*,[1] in adults over 60 years of age revealed that about 47% of the elderly population uses herbal drugs. The main reason for herbal drug usage is the belief that these drugs have lesser side effects.

Nazarine, *et al*, [258] have screened two hundred and sixty extracts from marine organisms collected from the Western & Eastern coasts of India, Lakshadweep and the Andaman and Nicobar Islands, for their effects on 3 isolated tissues of the guinea pig namely, the ileum, the uterus and the atrium with the aim of detecting any anti-spasmodic, oxytocic. uterine relaxant, ionotropic and antiarrhythmic activity. Antispasmodic activity was observed in 22 extracts, ecbolic activity (spontaneous contractions in isolated uterus) in 59 samples, uterine relaxant activity in 16 samples and antihistaminic and anti-5HT activity in 6 samples.

21.2. Toxicity studies

Toxicity studies[16] revealed that LD50 of the ethanol extract of *Vitex leucoxylon* leaf was more than 3 g/kg whereas that of the cold aqueous infusion was 1050 mg/kg. LD_{50} of the ethanolic extracts was found to be 1 gm/kg for *Ailanthus excelsa*, 350 mg/kg for *Toddalia asiatica* and 250 mg/kg for *Araucaria bidwilli* on oral administration, in rats[49].

Cerpegin, a furopyridine alkaloid isolated from the chloroform extract of *Ceropegia juncea* was found to be toxic at doses above 400 mg/kg and the mice showed excitation, irritability, convulsions and respiratory paralysis[30].

The effect of multiple doses of the petroleum ether extract of *Hygrophilia spinosa* on the haematological and biochemical parameters and hepatorenal functions of normal mice was evaluated[259]. The results showed that weekly moderate to high dose levels (above 40 mg/kg) and daily high dose (8 mg/kg) affected liver and kidney functions and metabolic and haematological parameters. Lower doses did not alter them.

Sharathchandra and Balakrishnamurthy[260] have studied the mode of action of *Cleistanthus collinus*, a toxic plant that is frequently implicated in poisoning. *Cleistanthus collinus* causes a depletion of thiol/thiol containing enzymes in most organs which results in its toxicity. Thiol compounds may act as antidotes.

Administration of the juice of *Lantana camara* leaves to rats resulted in a significant reduction in the total protein, globulin, absolute lymphocyte count and percent lymphocyte count. Significant increase in the relative weights of adrenals was also observed. High doses (1500 mg/kg) significantly inhibited granulomatous tissue formation in rats, similar to cyclophosphamide[96].

The polyherbal drug, Prostina, recommended for use in benign prostatic hypertrophy showed no toxic effects as seen on morphological, gross behaviour, body weight changes and histopathological, biochemical and haematological changes in rats upto doses of 450 mg/kg, which is 15 times higher than the recommended dose[261].

22. Elemental analysis of plants drugs/formulations

Various Indian medicinal plants *viz. Ocimum sanctum, Tinospora cordifolia, Azadirachta indica, Nerium andicum* (Kanher) and *Acorus calamus* (Vacha) were analysed for the presence of minor and trace elements by instrumental neutron activation analysis (INAA). Concentrations of 13 elements were determined. *Zinc,* manganese, and sodium were significantly higher in *Ocimum sanctum* leaves while *zinc* was higher in *Azadirachta indica* leaves. The therapeutic significance of these plants in restoring ionic balance has been discussed by the authors[262].

In a similar study, specific parts of several plants (fruits, leaves, stem, bark and roots) often used as medicines in the Indian Ayurvedic system have been analysed by Singh and Garg[263] for 20 elements (As, Ba, Br, Ca, Cl, Co, Cr, Cu, Fe, K, Mn, Mo, Na, P, Rb, Sb, Sc, Se, Sr and Zn) by employing INAA. The samples were irradiated with thermal neutrons in a nuclear reactor and the induced activity was counted using high resolution gamma ray spectrometry. Most of the medicinal herbs have been found to be rich in one or more of the elements under study. Similarly, elemental analysis of some herbal plants used in the control of diabetes has been done by the techniques

of Neutron Activation Analysis (NAA) and Atomic Absorption Spectroscopy (AAS). The elements Mn, Na, Cl, Al, Cu, Pb, Ni, Cr, Cd, Fe, Ca, Zn and Hg were found to be present in different plants in various proportions[264].

23. Modern correlates for standardisation

An attempt has been made by Uchil *et al* [265] to develop a battery of standardization tests using modern technology for commonly used organometallic preparations (bhasmas) and compare them with the Ayurvedic tests. Seven preparations of copper bhasma manufactured by different companies were screened using both the methods. The results revealed that only 3 preparations could fulfil at least 3 of 4 criteria as described in Ayurvedic textbooks. However, all of them differ with respect to particle size, bulk densities, copper content and presence of chemical groups and complexes when tested using modern correlates. None of them showed presence of elemental copper. These data reveal the necessity of development of modern correlates for standardisation of Ayurvedic formulation to add precision to quality control, to detect false claims and adulteration and to predict their adverse drug reactions.

24. Conclusion

We see a definite change in the pattern of research on medicinal plants. Our findings are listed below :

There is a growing interest in correlating phytochemical constituents of a plant with its pharmacological activity[266,267]. Scientists have even started correlating the botanical properties of plants with their pharmacological activity as seen from the work on by Rawat *et al* [146]. In future, more co-ordinated multidimensional research aimed at correlating botanical and phytochemical properties to specific pharmacological activities is expected.

In terms of pharmacological activity, more attention has been paid to CNS-active, cytoprotective, immunomodulators and chemotherapeutic plant products. Nutraceutics have opened up an entirely new field for exploration and, in the near future, dietary modulation of diseases may emerge as an alternative mode of therapy. At the same time a decreasing trend has been noticed towards evaluation of plants for their effects on the autonomic nervous system or fertility control.

With the advances in cellular biology, a shift towards studying changes in cytosolic enzyme activities, DNA patterns and genetic control has been observed rather than concentrating merely on the gross effects induced by the plant drugs,

In addition to the proper utilization of technological advances, a logical interpretation of the codified language of traditional medicine also becomes a necessity in order to further promote research in this field. The work done on rasayana group of plants[211] is a good example of the above statement. Here, the authors have attempted to interprete the word 'rasayana' in modern scientific terminology and have taken into consideration the advocated uses for this group of plants as per Ayurvedic textbooks while designing their research protocol. This understanding triggered the subsequent research work that was aimed at evaluating the immunostimulant potential of the rasayana group of plants and now, we have indigenous immunostimulants available, at affordable rates, in the Indian market.

However, there is a flip side too:

Very few articles published in the last 5 years have provided adequate information on the procedures adapted by the researchers for quality assurance of the plant products. Any publication related to phytopharmacology should ideally provide data on the authentication and standardisation of the plant products.

Not all the research areas selected by the scientists were relevant to needs of our country. Infections like tuberculosis, malaria, diarrhoea, AIDS and malnutrition are some of the major problems of our country. However, these areas have not been extensively explored.

Majority of the drugs are at the experimental stage and have to still undergo clinical trials. In 1982, Dr.Satyavati had expressed need for well planned clinical studies. 16 years later, the status has not changed. There is still a paucity of clinical studies which are carried out in randomized, controlled, double blind manner.

Today, concurrent consumption of drugs from different disciplies is a common finding. Very few studies, however, address the problem of drug interactions, if any. In view of this, two studies documenting

interaction of plant drugs with modern medicine are important from the clinician's point of view[26,58]. Similarly, the documented data on adverse drug reactions of plant drugs is also sparse.

A relevant point that arose while compiling this data and needs mention is the need for documentation of research activities and publications of results, whether positive or negative, in peer-reviewed journals. Although, work carried out on traditional medicine is presented in conferences and is available in the conference abstract books (data of which may or may not be complete) or published in local journals, these are not peer-reviewed and moreover this data is accessible to a select few. This results in lacunae while judging the current status of research on traditional medicine and leads to a false impression that not enough research is being carried out in this field. Hence, networking of the various research activities carried out by different scientists has now become the need of the hour in order to provide information about and access to research work done in different laboratories of the country.

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